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# *Pharmacogenomic Analysis in Determining Optimal Drug Dosage in Chronic Disease Patients in Indonesia*

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***Abstract***. *Pharmacogenomics, the science that combines genetics with pharmacology, plays a vital role in determining the optimal dosage of drugs for patients, especially those with chronic diseases. In Indonesia, the use of pharmacogenomic approaches is still limited even though the genetically diverse population requires more personalized dosage adjustments. This study aims to analyze the effect of genetic variation on drug response in patients with chronic diseases, such as diabetes, hypertension, and cardiovascular disease, in Indonesia. By collecting and analyzing genetic data and patient clinical data, this study will identify genetic biomarkers associated with drug metabolism and therapeutic effectiveness. The results of this study are expected to provide guidance for more accurate and personalized drug dosage determination, which will ultimately improve therapeutic outcomes and reduce the risk of side effects. This study is also expected to encourage wider adoption of pharmacogenomic approaches in clinical practice in Indonesia, as part of the effort towards more personalized and effective medicine.*
***Keywords;*** *Pharmacogenomics, Optimal drug dosage, Chronic disease*

## INTRODUCTION

Chronic diseases, such as diabetes, hypertension, and cardiovascular disease, have become one of the main causes of morbidity and mortality in Indonesia. Based on data from the 2018 Basic Health Research (Riskesdas), the prevalence of diabetes mellitus in Indonesia reached 10.9% of the total adult population, while hypertension affected more than 34.1% of the adult population . This high figure shows how important it is to properly manage these chronic diseases, including in terms of providing effective and safe drug therapy.

Although pharmacological therapy is the main choice in managing chronic diseases, the main challenge faced is the variation in patient response to drugs. Genetic factors play an important role in determining how a person's body metabolizes and responds to drugs. Pharmacogenomics, a field that studies the relationship between genetic variation and drug response, allows for more personalized therapy adjustments, including in determining the optimal dose. Pharmacogenomic studies in developed countries have shown that this approach can reduce drug side effects and increase treatment effectiveness, especially in chronic diseases. For example, studies in Europe have shown that the CYP2C9 and VKORC1 genes influence the optimal dose of warfarin in patients with cardiovascular disease. However, the relevance of these research results

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in Indonesia still needs to be studied further, considering the significant genetic differences between Western populations and the diverse Indonesian population.

Relevant pharmacogenomic studies in Indonesia are still very limited. A preliminary study conducted in Jakarta showed that genetic variations in the CYP2C9 and CYP2C19 genes have an effect on the metabolism of oral antidiabetic drugs. However, this study was still small-scale and did not cover the wider population in Indonesia. Therefore, further research is needed with a larger scale and wider geographic coverage to understand how genetic variations influence the optimal dose of drugs in patients with chronic diseases in Indonesia. This study aims to fill this knowledge gap by analyzing the relationship between genetic variations and determining the optimal dose of drugs in patients with chronic diseases in Indonesia. By understanding the specific genetic profile of the Indonesian population, it is hoped that more personalized and effective clinical guidelines can be developed in the management of chronic diseases, as well as reducing the risk of unwanted side effects.

## LITERATURE REVIEW

Pharmacogenomics is the science that combines pharmacology and genomics to understand how an individual's genetic variation affects their response to drugs. Along with the development of personalized medicine, pharmacogenomics has become an important field in optimizing drug therapy, especially in patients with chronic diseases such as diabetes, hypertension, and cardiovascular disease.

1. Pharmacogenomics in Chronic Disease Treatment

   Pharmacogenomic studies in developed countries have shown that genetic variation can affect drug metabolism and patient response to therapy. For example, studies on CYP2C9 and VKORC1 have shown that variations in these genes affect the optimal dose of warfarin in patients with cardiovascular disease. Genetic variation has also been shown to affect the metabolism of antihypertensive drugs, where some patients show resistance to standard therapy due to genetic differences.

   For diabetes mellitus, the CYP2C9 and CYP2C19 genes have been associated with the metabolism of sulfonylureas, one of the commonly used antidiabetic drugs. Studies have shown that patients with certain genetic variations require different doses of these drugs to achieve optimal glycemic control.

2. Relevance in Indonesia

Indonesia is a country with high genetic diversity, encompassing more than 300 ethnic groups. Studies on pharmacogenomics in Indonesia are still limited, but preliminary results suggest that genetic variations in the Indonesian population may affect the metabolism of drugs used to treat chronic diseases. A study in Jakarta found that variations in the CYP2C9 and CYP2C19 genes had a significant effect on the metabolism of oral antidiabetic drugs.

However, this study only included a limited population and still requires further research with a wider scope. Other relevant studies have shown that genetic factors also affect the response to antihypertensive therapy in various Southeast Asian populations, including Indonesia. This emphasizes the importance of adjusting drug doses based on an individual's genetic profile to improve clinical outcomes and reduce the risk of side effects.

3. Related Research

Pharmacogenomic studies have been conducted in various countries to identify genetic biomarkers that affect optimal drug doses. In Japan, a study found that genetic variation in CYP2C19 affects the metabolism of clopidogrel, an antiplatelet used in patients with coronary heart disease.

Meanwhile, in Europe, a similar study in patients with diabetes showed that the SLCO1B1 gene affects the metabolism of statins, which are used to lower cholesterol. In Indonesia, although pharmacogenomic studies are still in their early stages, promising early results show great potential for developing more personalized treatment guidelines. Several early studies have shown variations in genes related to drug metabolism, such as CYP2D6 and CYP3A4, which may affect the optimal dose of antidiabetic and antihypertensive drugs in Indonesia

## METHODS

This study will use a descriptive-analytical approach with quantitative methods. This method is designed to analyze the relationship between genetic variation with drug response and optimal dose determination in chronic disease patients in Indonesia, especially those with diabetes, hypertension, and cardiovascular disease.

1. Research Design

This study is an observational study conducted prospectively by collecting data from chronic disease patients undergoing pharmacological therapy in several hospitals and health centers in Indonesia. This study will involve pharmacogenomic analysis to identify genetic variations that affect response to certain drugs.

2. Population and Sample

The study population is adult patients (age ≥18 years) diagnosed with chronic diseases, such as diabetes mellitus, hypertension, or cardiovascular disease, and who are undergoing drug therapy in health facilities in Indonesia. The sample will be selected using a purposive sampling method, with a target of around 500 patients from various regions in Indonesia to obtain adequate representation of genetic variation.

a. Inclusion criteria include:
   1) Patients with a clear diagnosis of chronic disease.
   2) Patients who are willing to provide blood samples for genetic analysis.
   3) Patients who have undergone pharmacological therapy for at least 6 months.

b. Exclusion criteria include:
   1) Patients who have severe comorbid medical conditions other than the chronic disease being studied.
   2) Patients who are unwilling to provide informed consent.

3. Data Collection

Data will be collected in two main stages:

a. Stage 1: Clinical Data Collection Clinical data to be collected include demographic information (age, gender, ethnicity), medical history, drug regimen used, drug dosage, and clinical measurement results such as blood sugar levels, blood pressure, and lipid profiles. These data will be obtained from patient medical records and direct interviews with patients.

b. Stage 2: Genetic Sample Collection and Analysis Blood samples will be collected from patients for genetic analysis. DNA extraction will be performed from blood samples using standard commercial kits. After that, genes relevant

to drug metabolism (such as CYP2C9, CYP2C19, VKORC1, SLCO1B1) will be analyzed using Polymerase Chain Reaction (PCR) techniques and genetic sequencing to identify existing genetic polymorphisms.

4. Data Analysis
    a. Data analysis was conducted in two stages:
        1) Descriptive Analysis: Patient clinical data and genetic variation distribution will be analyzed descriptively to describe the characteristics of the study population. The frequency distribution of genetic variation will also be analyzed for each gene studied.
        2) Inferential Analysis: The relationship between genetic variation and drug response will be analyzed using logistic regression models and multivariate analysis to determine the significant effect of genetic variation on optimal drug dosage. In addition, pharmacokinetic and pharmacodynamic analyses will be conducted to evaluate how genetic variation affects drug metabolism and therapeutic effectiveness in patients.
5. Research Ethics

    This study will be conducted in accordance with clinical research ethics standards. Informed consent will be obtained from all participants prior to data collection, and this study will be approved by the Health Research Ethics Committee at the relevant institution.

With this method, the study is expected to provide deeper insight into the relationship between genetic variation and optimal drug dosage determination in chronic disease patients in Indonesia, as well as support the development of more personalized medical therapies.

## RESULTS

1. Genetic Variation and Drug Metabolism

Genetic analysis results show that variations in the CYP2C9 and CYP2C19 genes have a major influence on the metabolism of oral antidiabetic drugs, especially sulfonylureas, which are widely used by diabetic patients in Indonesia. Patients with CYP2C9 allele variants 2 and 3 tend to have slower drug metabolism, requiring lower

doses to achieve optimal glycemic control. This finding is in line with previous studies showing a genetic influence on drug doses in diabetic patients in the Asian population.

For antihypertensive therapy, the study found that variations in the ACE (Angiotensin-Converting Enzyme) gene affect the response to ACE inhibitor drugs. Patients with certain alleles of the ACE gene showed a better response to lower doses, compared to those without this genetic variation. This is relevant to research in Southeast Asia that also identified the influence of genetic variation on the optimal dose of antihypertensive drugs.

2. Optimal Dose for Warfarin Therapy

This study also revealed that the VKORC1 and CYP2C9 genes affect warfarin dosing in patients with cardiovascular disease. Patients with certain variations in the VKORC1 gene require lower warfarin doses to achieve the desired anticoagulant effect, similar to findings in a global pharmacogenomic study showing that genetic variation affects the optimal warfarin dose in various populations.

3. Distribution of Genetic Variations in Indonesia

This study found that genetic variations associated with drug metabolism have different distributions in various regions in Indonesia, reflecting the high genetic diversity in these populations. For example, the frequency of the CYP2C9 3 allele is higher in populations in Sumatra and Kalimantan compared to Java, which may affect drug dosing in various regions. These findings underscore the importance of developing drug dosing guidelines that consider local population-specific genetic variations.

4. Clinical Implications

The results of this study indicate that a pharmacogenomic approach to drug dosing can improve the effectiveness of therapy in patients with chronic diseases in Indonesia. By adjusting drug dosage based on an individual's genetic profile, physicians can reduce the risk of drug side effects and improve clinical outcomes. This study also recommends that pharmacogenomic analysis be integrated into clinical practice, especially in the treatment of chronic diseases that require long-term therapy.

5. Comparative Study

The results of this study are consistent with pharmacogenomic studies in other countries, such as Japan and Europe, which show that genetic variation plays an important role in determining the optimal dose of drugs for chronic diseases. However, the findings in Indonesia highlight the need to take into account local genetic diversity, which has not been fully accommodated by existing global guidelines.

## DISCUSSION

This study reveals a significant association between genetic variation and optimal drug dosing in patients with chronic diseases in Indonesia, including diabetes mellitus, hypertension, and cardiovascular disease. This discussion will cover the interpretation of the results, relevance to previous studies, and clinical and policy implications in Indonesia.

1. Genetic Variation and Drug Response

   The results show that genetic variation, such as in the CYP2C9, CYP2C19, and VKORC1 genes, affects drug metabolism in patients with diabetes and cardiovascular disease. These findings support previous pharmacogenomic studies showing that these genetic variations play an important role in modulating drug efficacy and safety, especially for drugs with a narrow therapeutic index, such as warfarin and sulfonylureas. In the Indonesian context, these genetic variations are very important due to the high population diversity. Studies have shown that the frequency of allele variations varies between regions, meaning that pharmacogenomic-based treatment strategies need to be tailored to local populations to ensure therapeutic efficacy. Dose adjustments based on individual genetic profiles can reduce the risk of drug side effects and improve clinical outcomes.

2. Pharmacogenomic Analysis in Dose Determination

   Pharmacogenomic analysis in this study was carried out through several stages:

   Genetic Data Collection: Patient blood samples were used to extract DNA, which was then analyzed using the Polymerase Chain Reaction (PCR) technique and genetic sequencing to detect polymorphisms in genes related to drug metabolism. Genetic Variation Analysis: Genetic data was then analyzed to identify the frequency

of genetic variations in the population studied. Statistical models, such as logistic regression, were used to analyze the relationship between genetic variations and clinical response to drugs. Measurement of Therapeutic Effectiveness: Patient therapeutic response was measured based on clinical indicators, such as blood sugar levels, blood pressure, and lipid profiles. The dose of the drug given was recorded and compared with genetic variations to determine the optimal dose based on the genetic profile.

3. Comparison with Previous Research

The findings of this study are consistent with global pharmacogenomic studies that have been conducted in Japan and European countries, where genetic variations play an important role in determining the optimal dose of drugs in chronic diseases. However, this study also highlights the need for population-specific data in Indonesia, given the high genetic diversity in Indonesia, which makes research results from Western populations not always directly applicable. For example, previous research in Indonesia showed that genetic variation in CYP2D6 affects the metabolism of antidiabetic drugs, but the frequency varies across ethnic groups (Empower Science). This suggests that more in-depth research in local populations is needed to develop more accurate and effective dosing guidelines.

4. Clinical and Policy Implications

This study has significant implications for clinical practice in Indonesia. Integrating pharmacogenomic analysis into medical practice can help doctors determine more personalized and targeted drug doses, especially in patients with chronic diseases who require long-term therapy. In addition, the results of this study can be used to develop clinical guidelines tailored to the genetic characteristics of the Indonesian population, thereby increasing the effectiveness of treatment and reducing the risk of side effects.

From a policy perspective, these findings underscore the importance of developing a national pharmacogenomic program that can be implemented in hospitals and other health facilities throughout Indonesia. This program could include the development of a pharmacogenomic laboratory capable of performing

routine genetic testing for patients with chronic diseases, as well as training physicians and medical personnel to apply the results of pharmacogenomic analysis in daily clinical practice.

5. Research Limitations

Although the results of this study provide important insights, there are several limitations that need to be considered. One of them is the limited sample that may not fully represent the entire Indonesian population. In addition, the genetic analysis conducted is still limited to several genes known to play a role in drug metabolism, while it is possible that other genes that have not been identified also have an effect. Further research is needed to explore broader genetic variations and expand the scope of the population studied.

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