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Investigate the Strategy of Using Pharmacogenetics and Pharmacometabonomics to the Personalization of Ticagrelor Antiplatelet Therapy

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ABSTRACT

Background: Ticagrelor is an oral antiplatelet agent commonly used to inhibit P2Y12 receptors that bind to it inversely. It is classified as cyclopentyltriazolopyrimidine (CPTP). Unlike prasugrel and clopidogrel, ticagrelor does not require metabolism activation. Thus, in theory, it is less affected by the variability seen with CYP polymorphisms and thus produces a more stable antiplatelet effect. However, clinical and laboratory experiments showed some defects in the P2Y12 receptor antagonism of ticagrelor. Despite awareness of many genetic and non-genetic variables that pose challenges to personalising ticagrelor treatment, most of its variable platelet reactions remain unexplained. Pharmacometabonomics, a process of discovering new biomarkers of drug response or toxicity in biofluids, have been used to predict drug response. The strength of using the pharmacometabonomics technique is that it forecasts a response and offers extensive knowledge on the metabolic pathways of a response. Integrating pharmacogenetics with pharmacometabonomics provides insight into unknown response-related genetic and non-genetic factors.

Method: The literature on the factors associated with the variable platelet reactivity of Ticagrelor was reviewed and the possible role of pharmacogenetics and pharmacometabonomics in the personalization of antiplatelet therapy with ticagrelor was discussed.

Result: This review identified that pharmacometabonomic techniques are not presently used to predict the response to Ticagrelor. It also demonstrates that the use of pharmacogenetics alone to test the response to Ticagrelor has limitations.

Conclusion: This study concluded that it is possible to use a combination of pharmacogenetics and pharmacometabonomics to predict the outcome of treatment with Ticagrelor.

Keywords: Pharmacogenetics, Ticagrelor, Pharmacometabonomics, antiplatelet therapy, personalized therapy

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INTRODUCTION

Ticagrelor is a platelet inhibitor that reversibly binds with the platelet P2Y12 adenosine diphosphate (ADP) receptor, and it does not have to be metabolically stimulated to inhibit the p2y12 receptor. It is also a selective treatment for inhibiting P2Y12 receptors and provides faster and more significant platelet aggregation inhibition than clopidogrel. Found in a trial of PLATO in adult patients with acute coronary syndrome (ACS), ticagrelor was more effective than clopidogrel over a period of 12 months [1,2].

The most common P2Y12 inhibitor utilized in patients with ACS is clopidogrel [3]. However, the drug needs to be activated in the liver by a cytochrome enzyme (CYP). It is also slow to act and susceptible to genetic polymorphism. In addition, clopidogrel has a wide range of interactions with many drugs, which has led to the production of new anti-platelet agents, such as ticagrelor. Some patients who use ticagrelor may have increased incidents of bleeding, mild to moderate shortness of breath, and ventricular pauses, which hinder optimum ticagrelor results. There are both genetic and non-genetic factors that contribute to the response to ticagrelor. Current methods for predicting response and identifying adverse events for ticagrelor do not adequately predict a therapeutic outcome [2,4,5]. Therefore, the search for new ways to assess the response and identify adverse reactions to ticagrelor could help achieve the desired effect after PCI. This paper reviews the literature on the use of pharmacometabonomics and pharmacogenetics approaches in furthering the evaluation of ticagrelor therapeutic outcomes.

Ticagrelor Bioactivation

Ticagrelor is an oral drug that is rapidly absorbed in the intestine (Figure 1). It appears that the average absolute bioavailability of ticagrelor is 36%, and the percentage of absorbed ticagrelor decreases further down the gastrointestinal tract. The mean area under the curve (AUC) for ticagrelor was found to be 89% in the proximal small intestine, 73% in the distal small intestine and 32% in the ascending colon of the mean AUC for orally administered suspension [6]. The steady-state volume for ticagrelor is 88 liters, and the average Tmax to active metabolite AR-C124910XX is 2-4 hours [7,8]. In addition, ticagrelor and AR-C124910XX have been found to be strongly bound to plasma proteins after absorption (more than 99.8%) and are mainly restricted to plasma space. [9].

For activation, the absorbed drug does not need further biotransformation. It binds reversibly and directly to the platelet ADP P2Y12 receptors, altering these receptors' conformation. Such binding prevents the activation and subsequent aggregation of platelets [10]. Ticagrelor and AR-C124910XX were both found to have a mean removal half-life of 6.7-9.1 hours and 7.5-12.4 hours respectively. Ticagrelor is excreted mainly in feces (58%), while

kidney excretion plays a secondary role (27%) [9]. Several in vitro experiments were performed to test the metabolism of ticagrelor in liver cells and microsomal preparations in various animal species [11]. A large number of metabolites were detected, and among them, AR-C124910XX and AR-C133913XX were the primary metabolites in all the organisms tested. Cytochrome P450 (CYP3A4/3A5) was responsible for the formation of AR-C124910XX. AR-C133913XX was most likely formed through CYP3A4, and CYP3A5 contributed less [12, 13]. Therefore, possible interactions in ticagrelor involving CYP3A4 were assessed have been evaluated in clinical pharmacology studies.

In turn, the drug interaction explains the common side effect of shortness of breath, which occurs in more than 13.2% of patients with ACS. Symptoms can include tightness in the chest or difficulty breathing. Another common side effect is the risk of severe bleeding, in 10.3% of patients, which includes severe uncontrollable bleeding, vomiting of blood or vomit that looks like ground coffee, pink, red, or brown urine, stools that are colored like red or black tar, coughing up blood, or blood clots [14, 15]. Other adverse symptoms include high blood pressure, nausea, cough, and diarrhea.

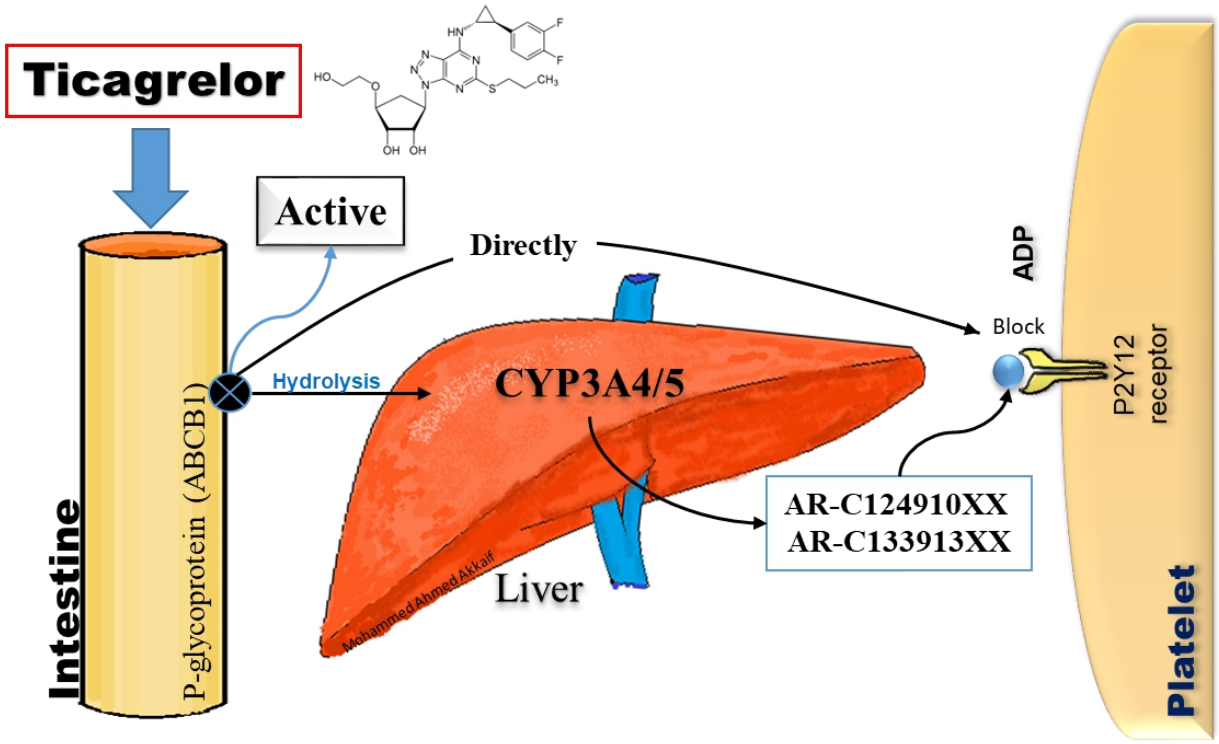

Figure 1: Ticagrelor Bioactivation.

The drug does not require biotransformation for activation. Nevertheless, part of it is metabolised in the liver and converted to an effective compound as powerful as the initial drug by hepatic cytochrome. It directly binds in reverse to the P2Y12 receptor on platelets, which alters the shape of these receptors preventing platelet activation and accumulation.

Drug Interactions mechanism

Ticagrelor can be quickly absorbed when consumed orally, and the highest blood concentration can appear in 1.5 hours [16]. After being catalyzed by metabolic enzymes, ticagrelor can shape more than 10 different metabolites [9]. AR-C124910XX, which is primarily formed by CYP3A4 and 3A5, is the primary active metabolite. Unlike thienopyridine antiplatelet drugs, both the parent compound and the AR-C124910XX active metabolite have clear antiplatelet effects. The AR-C124910XX accounts for 30%-40% of the ticagrelor metabolites [9, 17], while another major metabolite is AR-C133913XX, which does not have an antiplatelet effect [9]. Therefore, when ticagrelor and CYP3A inhibitors or inducers are used simultaneously, drug interactions may occur [9].

CYP3A accounts for more than half of CYP enzyme subtypes, including CYP3A4 and CYP3A5. There is a large amount of CYP3A in the intestinal epithelium and liver. Because it involves more than 50% of the oxidation reactions of clinical drugs and from all the drug-metabolizing enzymes, CYP3A seems to be the most significant. In vitro experiments showed that ticagrelor and AR-C124910XX could slightly inhibit the activity of CYP3A, and they are both substrates of CYP3A4 [18, 19]. Ticagrelor co-administration with a rifampicin CYP3A inducer increased ticagrelor clearance by 110%, decreased Cmax by 73% and decreased ticagrelor efficacy. Therefore, co-administration of ticagrelor with inducers of CYP3A4 is not recommended (rifampin, phenobarbital, phenytoin, carbamazepine, and dexamethasone) [20].

In a case report of a patient with coronary artery disease (CAD), the patient was previously taking phenytoin and began treatment with ticagrelor after a stent was placed. The study revealed less platelet inhibition in a patient after taking ticagrelor. When phenytoin intake was stopped, platelet inhibition improved [21].

In a study by Chong J. et al., 2020 mouse liver microsomes were used to examine the drug interaction between rivaroxaban and ticagrelor in vitro. The results showed a drug-drug interaction between ticagrelor and rivaroxaban in mice. The researcher recommends that studies should be conducted to verify the occurrence of similar reactions in humans [22].

The value of P-glycoprotein, a protein responsible for the biological transport of most drugs and expressed in the small intestine, liver cells, kidneys, and the blood-brain barrier, has been recommended by numerous studies. P-glycoprotein is a transporter substrate for ticagrelor, and any agent that inhibits P-glycoprotein activity contributes to a decrease in the efficacy of the original drug [9, 23]. The combined use of ticagrelor and digoxin, for which P-gp is the primary transport substrate, increased the concentration of digoxin in plasma (Cmax by 75%, AUC by 28%) [24]. Therefore, it is recommended that patients receiving P-gp-based drugs be monitored when ticagrelor is administered.

The role of pharmacogenetics biomarkers in clinical outcomes of ticagrelor

A vital marker is a biological indicator of a disease, clinical condition, or response to treatment and is evaluated for indicative accuracy [25, 26]. Similarly, as a biomarker for this event, genetic variants associated with the biological event could be used. Some studies have been conducted to investigate the effect of clopidogrel treatment on platelets and inadequate antiplatelet effects in up to one third of patients treated with clopidogrel [27-30]. The genetic variation of CYP2C19 and ABCB1 is one of the most probable explanations for variability in clopidogrel response. The CYP2C19 genotype influenced the antiplatelet behavior of platelets in the combined study of React and ONSET/OFFSET, while the platelet activity of ticagrelor was not correlated with the genotype of CYP2C19. Regardless of the CYP2C19 genotype, ticagrelor displayed less platelet reactivity (less platelet aggregation) than clopidogrel in all assays used in the analysis.

The platelet response of ticagrelor or clopidogrel treatment groups was not significantly affected by the ABCB1 genotype [28, 30]. As part of a PLATO analysis, a major genetic sub-study was carried out. This sub-study showed that the types of polymorphisms CYP2C19 and ABCB1 were independent of the lower rates of cardiovascular or MI death or stroke found in patients treated with ticagrelor compared to clopidogrel. [31, 32]. The PLATO research also found that an increased frequency of non-procedural bleeding after PCI was associated with the use of ticagrelor [14]. One study found that CYP4F2 rs3093135 TT variant carriers had a greater effect on inducing frequent non-procedural bleeding during ticagrelor therapy compared to AA and AT variant carriers, with regard to bleeding events that may occur in some individuals taking ticagrelor [33].

In another study, CYP2C19*2A, was significantly associated with decreased Cmax. Tmax of ticagrelor for the wild CYP2C19*1 was substantially higher than for variant types. CYP2C19*2 and CYP2C19*3 appear to be among the most clinically essential alleles in Chinese individuals [34]. It was found that the incidence of the CYP2C19 variant was much higher in Asians (10-25%) than in whites and Africans [35]. The difference between individuals shows a 30-90% difference in CYP3A activity to genetic variants [36, 37]. Therefore, an understanding of ticagrelor's genetic determinants could improve treatment strategies and enhance individual P2Y12 inhibitory therapies depending on gene variants.

Potential role of pharmacometabonomics in personalized therapy

In many drug therapies, assessing drug response is either difficult or time consuming for a response to be detected. This hinders therapy optimization. To predict drug responses, the term pharmacometabonomics was therefore proposed [25, 38]. In some literature, pharmacometabonomics, or pharmacometabolomics, is a metabonomics study that aims to discover novel metabolome biomarkers associated with drug response or toxicity [27, 39-41]. These new biomarkers may be used as a classification method for classifying patients who are drug-responsive or non-responsive or who may or may not experience drug toxicity [28, 42]. Not only is the metabotype of pharmacological response a prediction of the response of the patient, it also reveals metabolic pathways. It tracks the patient during the disease management process, which contributes to the personalization of care [28, 42-44]. Similar to metabonomics, pharmacometabonomics represents not just the difference in genes, gene function, and expression of proteins, but also the interaction with them in the environment [45, 46]. In fact, pharmacological response prediction software is economical and less invasive [4, 47].

Clayton *et al.,* 2006, first suggested the term. Using proton nuclear magnetic resonance (1H-NMR) spectroscopy, urine samples of rats pre-and post-dose with 600 mg of paracetamol were analyzed to identify a metabotype associated with paracetamol-induced hepatotoxicity. A pre-dose high level of taurine associated with the mean histology score (MHS) was shown to be used to estimate liver damage [25, 38]. However, pre-dose, low trimethylamine-N-oxide (TMAO) and betaine levels have been associated with increased liver damage induced by paracetamol. A repeat of the study in healthy volunteers showed that high pre-dose levels of urinary cresol sulphate were associated with low post-dose urinary ratios of acetaminophen sulphate to acetaminophen gluconate (S/G) due to the sulfotransferase enzyme competence of acetaminophen and 7-cresol [31, 44]. Therefore, an endogenous high p-cresol level causes an increase in liver susceptibility to acetaminophen hepatotoxicity and allows the use of the form of urine sulphate as a predictive pre-dose biological indicator.

Studies in pharmacometabonomics have also been developed to use various models to classify metabotypes of drug efficacy and toxicity in tissues, organisms, and humans [48-52]. Metabolomics is only one of the biological variability chains that may lead to drug response differences between individuals. The findings of some pharmacometabonomics studies in humans are summarised in Table 1. Previous research, including a special platelet metabolome analysis, has shown that metabolites are important as indicators of platelet biological function [53-55]. Therefore, platelet metabolism can determine the ticagrelor response through a pharmacometabonomics test.

Table 1. Examples of pharmacometabonomics studies in humans

Study	Drug	Analytical Method	Specimen	Main findings
Holmes *et al.,* 2006 [43]	Antipsychotic drugs*	1HNMR	CSF	This study examined the kind of schizophrenia metabolism that separates naive antipsychotic medication patients from healthy subjects. After short-term therapy with antipsychotic medications, this metabolic trend was reduced to normal in half of the patients.
Clayton, T.A., *et al.,* 2009 [44]	Acetaminophen	1HNMR	Urine	Large urinary p-cresol sulphate pre-dose levels had a low urinary post-dose ratio of acetaminophen sulphate to acetaminophen glucuronide.
Backshall, A., *et al.,* 2011 [56]	Capecitabine	1HNMR	Serum	Subpopulations prone to capecitabine toxicity in inoperable colorectal patients are defined by baseline metabolic profiles.
Villasefior *et al.,* 2014 [57]	Ketamine	LC-TOF-MS	Plasma	This study identified discriminatory metabolites among patients with bipolar depression between responders and non-responders of ketamine. Discriminating metabolites are linked to mitochondrial fatty acid β -oxidation.
Elbadawi *et al.,* 2016 [58]	Simvastatin	GC–TOF–MS	Plasma	The initial signature of simvastatin-induced insulin resistance was established, including ethanolamine, hydroxylamine, hydroxy carbamate, and isoleucine, which may be predictive biomarkers of individual susceptibility to simvastatin that promotes another type II diabetes mellitus outcome.
Amin *et al.,* 2017 [53]	Clopidogrel	1HNMR	Urine	Sixteen metabolites were associated with clopidogrel HTPR in pre-dose samples. In post-dose samples, however, 18 metabolites were associated with HTPR clopidogrel. The function of the intestinal microbiota involved in clopidogrel HTPR was also shown.
Park *et al.,* 2018 [59]	Metformin	GC/MS	Urine	The identified metabolites, myoinositol, citric acid, and levels of hippuric acid, showed particularly significant variation between the responder and non-responder groups, thereby identifying various metabolite profiles in two groups of diabetes mellitus type II patients after using pharmacometabolomics as metformin administration. These findings might provide better understanding and metformin response prediction and its variability in patients.
Bawadikji *et al.,* .2020 [60]	Warfarin	1HNMR	Plasma	In distinguishing between stable INR and unstable INR, the findings of this research indicated that alpha and beta glucose can be used as biomarkers of unstable INR in plasma.

Pharmacometabonomics-aided pharmacogenetics

There is no new notion of the positive pairing of "-omics" technologies. Pharmacogenomics and pharmacometabonomics complement each other and thereby improve the recognition of associations that are clinically important. Genotype imputation was able to distinguish genetic variants of interest in pathways that were found during pharmacometabolomics studies rather than traditional tag SNP genotyping [61-64]. This approach expedites and extends the scope of the study of candidate genes for pharmacogenomics. This theory is based on the premise that changes in genes or gene expression can lead to changes in proteins. The metabolite levels associated with these pathways eventually change [56, 65].

The integration of pharmacogenetics and pharmacometabonomics has the advantage of getting more extensive and comprehensive information on variations in drug response. For instance, combining these two methods has revealed more knowledge on aspirin response variation [66]. Using metabolomics, associations between aspirin response and the purine pathway were found. This led to further investigations into the SNP gene involved in the purine pathway, which led to the discovery that the SNP was linked both before and after aspirin action to concentrations of a number of purine metabolites. Consequently, a new genetic locus that may function in person variation in response to aspirin was established through the use of both genomic and metabolomic analyses [67].

What is expected, beyond data mining and analysis, is to merge omics and information technology. A synergy between artificial and human intelligence is therefore proposed to (i) acquire pharmacometabolomic and pharmacogenomic data and thus resolve the interplay of genomic and environmental factors, (ii) promote collaborative analysis of data, and (iii) direct the rapid and efficient processing of data through sensory decision making. Technical developments have made it possible in recent decades to shift to wider studies of large-scale "-omics" data involving genomics, transcriptomics, proteomics, and metabolomics. A schematic representation of the effect of the microbiome and other aspects of the environment on the metabolome is

integrated in Figure 2. Each of these omics methods moves us independently to wider, less-biased research that can uncover novel pathways underlying disease pathophysiology and drug therapy response.

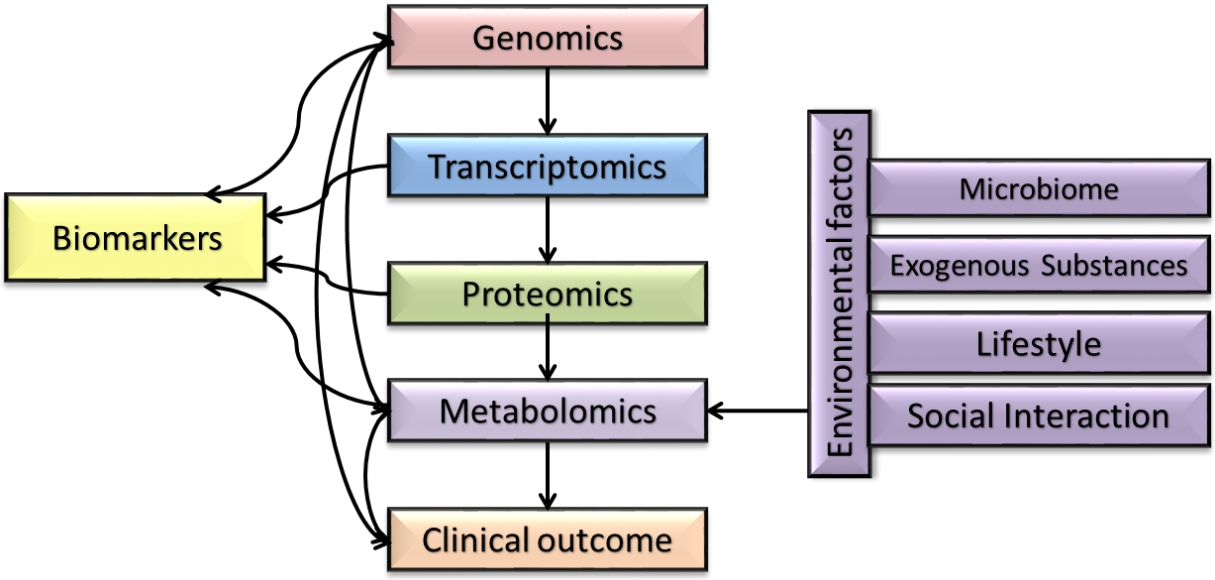

Figure 2: Pharmacometabonomics-aided Pharmacogenetics.

This figure demonstrates how the items can collectively provide biomarkers for phenotypes (disease or clinical condition or drug response biomarkers).

This essential system, based on the collection of important elements and mechanisms, is a standard by which a method can be developed, and an approach could be investigated and accepted by the informatics community and/or biomedical scientists, paving the way for better-informed and cost-effective studies. In addition to detailed review and interpretation, "-omics" data requires extreme filtering. At the same time, biomedical scientists must cooperate and make decisions effectively and efficiently [68]. As a result, large-scale quantities of complex multi-faceted data need to be processed, extracted, and analyzed in a meaningful manner. A groundbreaking web-based collaboration support platform offered by Tsiliki *et al.,* (2014) adopts a hybrid approach based on the synergy between artificial and human intelligence. Acquired data on reaction biomarkers can help to recognize obscure genetic variations. These biomarkers of response can be used as an economic instrument to classify both the response and the probability [69].

CONCLUSION AND PERSPECTIVES FOR THE FUTURE

Despite the reality of physiological differences between individuals, drug development and patient care have been dependent on the same system for different population groups, resulting in serious adverse events from patients' low levels of drug response. Understanding the individual and pharmacokinetic differences of antiplatelet agents is important for guiding treatment as well as avoiding drug interactions and providing optimal doses. The era of precision medicine is expected to have a decisive word in guiding appropriate treatment for patients based on their vital signs. This, in turn, helps explain phenotypes and personalize ticagrelor therapy. By looking at future studies to direct the appropriate treatment using one of the aforementioned basic systems, this study found that it is a feasible way to direct individual treatment. However, the researchers noticed that it cannot provide sufficient information to make drug treatment accurately targeted. We are gradually moving to integrate these systems and recommend that future studies be based on the use of multiple methods to classify phenotypes and variations in response to drugs. The researchers also stress the importance of focusing on the integrative pharmacometabonomics with the pharmacogenomics approach, which in turn enhances the understanding of biochemical pathways of treatment. This approach may move to the identification of genetic and metabolic variants that may contribute to inter-population differences in treatment-directed responses.

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Contributions:

B.I and M.A.A. conceived this research and designed Study; B.I., A. S., N.A.A.D., M. A.A. analysis and interpretation of

data and drafting the manuscript and the final approval of the version to be published

Conflicts of Interest: The authors declare that they have no conflicts of interest.

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