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THE POTENTIAL IMPACT OF PHARMACOGENETICS ON PERSONALIZED MEDICINE AND MEDICATION COMPLIANCE: A REVIEW

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ABSTRACT

The expansion of gene cloning, DNA genotyping and sequencing have greatly influenced the enlargement of the applications of Pharmacogenetics in drug discovery and development. It is used to unveil inherited genetic alterations in different drug metabolic pathways leading to varied pathological and therapeutic response. Personalized medicine is a medical model that tailor therapy with the best response and maximum safety limits to secure better patient care. It is tailored to the different characteristics of individual patients that is relied on person's distinctive genetic and molecular profile making them vulnerable to different diseases. However, therapeutic response is largely dependent on medication compliance that generally describes the extent to which patients correctly take medications by strictly obeying to the medical advises. In addition, it is based on the factors such as getting prescriptions filled, remembering to take medication on time, correct use of home medical devises, self-directed exercises, self-care, therapy sessions, and comprehending the directions.

KEYWORDS: Pharmacogenetics, personalized medicine, medication compliance.

1. INTRODUCTION

Pharmacogenetics is the study of inherited genetic differences in drug metabolic pathways that influence individual person's responses to drugs, both in terms of therapeutic and adverse effects.[1] The term pharmacogenetics is generally used interchangeably with the term pharmacogenomics which aims investigating the role of acquired and inherited genetic variations in relation to drug response and drug behavior by systematic examination of the inter- and intra-individual variation in gene expression.[2] Currently, application of pharmacogenetic principles in drug prescribing has become clearer due to the expansion of gene cloning, DNA genotyping and DNA sequencing. Personalized medicine is a good example for application of pharmacogenetics to comprehend the way of benefit individuals from specific drugs.

2. Personalized medicine

Personalized medicine is a medical doctrine that divides people into different groups which is based on medical practices, medical decisions, interventions and/or drugs being personalized to the individual patient depending on their risk of disease or predicted response.[3] The concept of personalized medicine is an essential prerequisite for the future prospects of making worthy medical care. It can be used to develop and validate new targeted therapies, with more specificity and efficacy to treat patients. Under this notion, the disease predisposition can be determined more accurately by using molecular data to better describe the disease, with fewer adverse events.[3]

Pharmacogenetics research supports the development of personalized medicines via demonstrating how a person's genes affect for different medications with long-term goal of supporting medical officers to select the drugs and doses as best suited for each person. It generally refers how variation in one single gene impacts the response to a single drug. Genetic variation in metabolism may result in high concentrations of drugs and an increased risk of adverse effects in slow metabolizer drugs such as antidepressants or chemotherapy.[3,4] Hence, the essential information on

person's genetic makeup, or genome, selection of drugs and their doses that is likely to work best for a particular person can be determined through pharmacogenetics research studies. This field of pharmacogenetics combines the pharmacology with the genomics.[4]

2.1 Genetic polymorphism and drug response

It is evidenced that most of the human genes with casual variations of the nucleotide base sequence are developed during the course of evolution. Genetic mutations relating to single base pair substitutions are the simplest genetic variations, which is defined as single nucleotide polymorphisms (SNPs). Single Nucleotide Polymorphisms (SNPs) typify the most communal type of genetic variation within the human population, with a frequency of one in every 100–300 nucleotides. It accounts for about 10 million SNPs in the human genome.[5] The identification and characterization of the SNP based 'genetic profile' can be represented as a 'fingerprint' that helps to define the hazard of an individual's susceptibility to various diseases and response to drugs.[5]

Genetic mutations may also implicate more than one nucleotide or lengthy DNA traits. In this circumstance, they reflect large mutations that are defined as deletions, inversions, duplications and translocations.[6] Mutations found in a codifying area lead to a substitution of a specific amino acid in the respective location of a protein via influencing the protein function. However, the variations arise in a regulatory region affect transcription and translational machineries leading to an altered gene expression level.[7] If genetic variations in nucleotide sequences in a population reflect a 1% allele frequency or higher, these variants are called as polymorphism. On contrary, variation categorized by less frequency is named as a mutation. Both mutations and polymorphisms encode for enzymes categorized by diverse metabolic activity or receptors involving varied affinity for different drugs. Consequently, this event alters the pharmacological response to various drugs in individuals or, in some ethnic parties or in a population.[6,7] The polymorphisms of genes encoding for proteins/enzymes linked with metabolism of the drug cause distinct individual responses to the drug. Table 1 displays some examples of genetic polymorphisms that affect specific drug responses in humans.

Table 1: Variations in drug responses in humans influenced by genetic polymorphisms. (Table was embedded at the end of the manuscript).

Name of the Drug	Genes with associated mutation	Mechanism	Clinical effect
Fluorouraci	DPD (exonic mutation)	Abrogation of enzymatic activity	Increases toxicity
Warfarin	CYP2C9 (coding region variants)	Reduction of S-warfarin clearance	Upsurge anticoagulant effects
	VKORC1 (variant haplotypes in regulatory regions)	Alteration of gene expression	Decrease anticoagulant effects
Statins (HMG-CoA reductase inhibitors)	HMGCR	Alteration of HMG-CoA reductase activity	Decrease LDL cholesterol
Diuretics	Adducin (adducin variants)	Alteration of cytoskeletal function	Reduce Blood pressure
Abacavir	HLA variants	Alteration of immunologic responses	Immunologic reactions
Irinotecan	UGT1A1 (regulatory polymorphism)	Reduction of gene expression	Increase hematopoietic toxicity
Omeprazole	CYP2C19	Hypofunctional alleles	Resulting Peptic ulcer
Antidepressants, β-blockers	CYP2D6	Hypofunctional alleles	Increase toxicity
		Gene duplication	Reduce activity
HIV protease inhibitors, digoxin	ABCB1 (MDR-1)	Alteration of P-glycoprotein function	Decrease CD4 response in HIV-infected patients, and decrease digoxin bioavailability
Azathioprine (AZA)	TPMT variants	Inactivation of toxic products produced from azathioprine (AZA) metabolism.	Hematological toxicity of 6-mercaptopurines.

2.2 The fate and disposition of drugs

The fate and disposition of various drugs inside the human body and their therapeutic effect are based on complex event of codifying proteins by varied genes leading to influence the drug transport, machinery of action and metabolism.[8] Drugs must reach the target in the human body in sufficient concentration, and reside there in a bioactive form long enough for the execution of biological events to work out as a drug. Thus, drug development process involves assessment of absorption,

distribution, metabolism excretion and Toxicity (ADMET) of that targeted substance inside the body.[8,9] Drug discovery is a multifarious process with the aim of determining efficacious molecules where their selectivity and strength are balanced with ADMET properties to find out the fitting dose and dosing interval.[9]

P-glycoprotein (P-gp) is encoded by the multi-drug resistance (lMDR1) gene that influences drug pharmacokinetic and pharmacodynamic. Drug metabolizing enzymes are considered as monooxygenase or mixed-function oxidase including cytochrome P450, NADPH-cytochrome P450 reductase and cytochrome b5.[10] Cytochrome P450 (CYP) is reflected as major drug metabolizing enzymes mainly CYP2D6, CYP2C19, CYP2C9, CYP3A4 and CYP3A5 isoforms. CYP proteins and P-gp/MDR1 proteins are localized at the apical/luminal membrane of enterocytes.[10,11] P-glycoprotein (P-gp) is considered as an efflux transporter which carry drug molecules from the cell cytoplasm and transport back into the intestinal lumen to excrete. P-gp/MDR1 and CYP3A proteins are major protective barriers for the bioavailability of orally administered drug molecules synergistically. As depicted in Figure 1, the organic anion transporting polypeptide (OATP) and organic cation transporting polypeptide (OCTP) are uptake transporters that mediate the transport of molecules into the cell.[11]

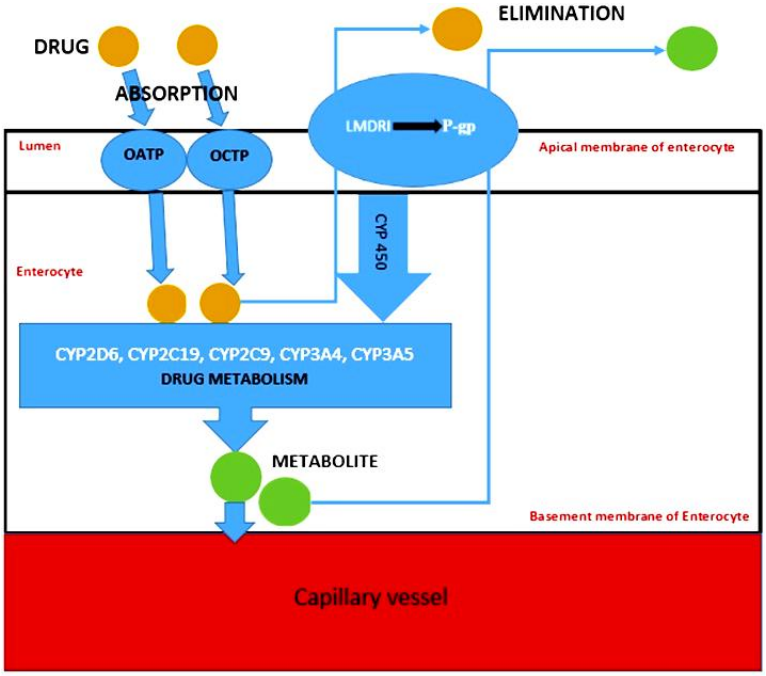

Figure 1: The depiction of the causal link between P-gp/ MDR1, CYP proteins and Bioavailability and Drug metabolism. Absorption, transportation, metabolism and elimination of drug substance are displayed in the small intestinal Enterocyte.

When a drug becomes a substrate of P-gp and CYP3A4, it is diffused through the enterocytes to gain access to the systemic circulatory system. P-gp and CYP3A4 act as barriers to the systemic exposure of drugs. Some drug molecules will be transported out of the enterocyte by P-gp and be eliminated without absorption (Figure 1). Other molecules will be metabolized by CYP3A4 in the enterocyte and lost to pharmacologic activity.[12] P-gp promotes the modulation of the number of drug molecules in the enterocyte and therefore prevent saturation of CYP3A4. This results in an increase in the efficiency of first-pass drug metabolism. CYP3A4 concentrations decrease from the proximal to distal portions of the intestine. P-gp content increases from the proximal to distal intestine. Thus, where an excess of CYP3A4 is available for metabolism, less P-gp is present. Conversely, where CYP3A4 concentrations are lower, more P-gp is found to prevent saturation of the enzyme.[13,14]

Inhibitors of P-gp will enhance the bioavailability of a P-gp substrate, whereas inducers of P-gp will decrease the bioavailability of a P-gp substrate drug. Although digoxin drug is a substrate of P-gp, it is not metabolized by CYP3A4. P-gp inhibits its bioavailability and contributes to its renal and biliary secretion. Further, P-gp can control the access the drugs towards CYP metabolizing enzyme that results in increased metabolism from prolonged exposure to the enzyme through repeated cycles of absorption and efflux.[15,16] However, P-gp activity can be increased due to various factors such as drug interactions or genetic mutations of the MDR1 gene. The localization of P-gp/ MDR1 and CYP3A represents that the quantity of substrates metabolized by the CYP3A enzyme can be controlled by P-gp/MDR1.[17,18] Among several families of CYP proteins, CYP1, CYP2, CYP3 and CYP4 are the most essential proteins in terms of drug biotransformation;

particularly CYP3A4, act as the most prevalent CYP in the body and involves in metabolizing many drugs.[19]

2.2.1 CYP2D6 polymorphism

Genetic variation in pharmacogenes leads to modulate and control the drug absorption, distribution, metabolism and excretion (ADME) influencing drug response and the risk of adverse drug reactions. Numerous variations or polymorphisms occurred in the genes that encode CYP and other drug metabolizing enzymes (DMEs), drug transportation genes and genes that code for protein receptors and other effectors track therapeutic variations in drug response. Metabolic activity of different CYP enzymes is detected by using selective substrate of distinctive CYP enzyme as a marker of metabolic activity.[42] The marker substance should be non-toxic, in view of its possible *in vivo* use, easily available and assessable in biological fluids with its major metabolites. Drug metabolizers are divided in to 4 different groups namely ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers and poor metabolizers based on the phenotype.[43]

A striking example for this includes ultrarapid metabolism of codeine by CYP2D6 with toxicity owing to CYP2D6 polymorphism; Codeine is an opiate analgesic drug which is used to treat pain, cough and diarrhea. However, codeine must initially undergo o-demethylation by CYP2D6 resulting the product morphine in order to exert its opioid activity.[20,21] CYP2D6 plays a major role through conversion of 5-10% of codeine in to morphine that act as the active metabolite of codeine. The remaining 80 % of codeine are being converted in to inactive metabolites and excreted (Figure 2). Individuals who carry two normal function copies of the CYP2D6 gene are able to metabolize codeine in to morphine that is adequate to exert pain relief. In spite of that, individuals who carry at least 3 normal function copies of the CYP2D6 gene are able to metabolize codeine more rapidly in to morphine increasing the risk of morphine overdose with much side effects too.[22,23] Codeine intoxication or death has been reported in several studies that use codeine in children and adults with ultra-rapid *CYP2D6* activity.[44] In addition, when ultra-rapid metabolizers are treated with codeine, it was reported to owe symptoms such as shallow breathing, sleepiness and confusion. Therefore, it is recommended to prescribe a lower dose to such patients. Patients with *CYP2D6* poor metabolizers do not attain adequate pain control due to the incapability of drug to convert to its active form of morphine.[44]

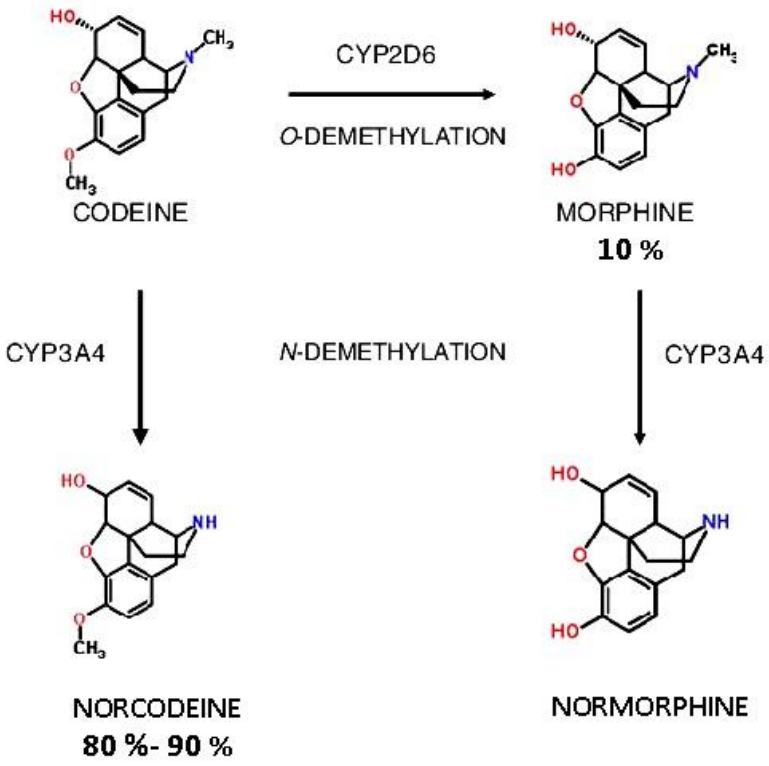

Figure 2: Ultrarapid metabolism of 5-10% of codeine in to morphine from O-Demethylation by CYP2D6 with toxicity owing to CYP2D6 polymorphisms. The remaining 80 % of codeine are converted in to inactive metabolite Norcodeine.

Genetic variation in pharmacogenes is further exemplified by the effect of CYP2C19 polymorphisms on the response towards clopidogrel or proton pump inhibitors.[24,25] Clopidogrel is an antiplatelet medicine

used to reduce the risk of stroke and heart disease and proton pump inhibitor (PPI) drugs are used to make a long-lasting reduction of stomach acid production. PPI drugs generally prescribed during the course of clopidogrel owing to associated risk of gastrointestinal bleeding. The patients who carry loss-of-function allele of CYP2C19 polymorphism are known to display comparatively low responses to clopidogrel with proton pump inhibitors.[26]

The patients with poor CYP2C19 metabolizers were more likely to have a subtherapeutic antiplatelet response under the treatment with clopidogrel and increasing the risk for cardiovascular adverse events.[45] Several clinical trials were performed to determine the right dose of clopidogrel drug for patients with CYP2C19-compromised.[45] However, it was failed to publish consistent findings implying other factors are also involved in predicting adverse clinical reactions and efficacy of the drug. Nevertheless, another study has demonstrated that CYP2C19*2 heterozygotes under the treatment of threefold higher doses exhibited notably reduced platelet response, compared to noncarriers treated with regular maintenance doses.[46]

2.3 Epigenetic side-effects of Pharmaceutical drugs

Epigenetic side-effects of commonly used pharmaceuticals have become a potential new field in medicine. In other words, the chemicals that contained in the drugs can cause persistent epigenetic changes. These alterations of epigenetic homeostasis can be arisen through direct or indirect mechanisms. Direct effects can be resulted due to the pharmaceutical drugs that influence the chromatin architecture or DNA methylation.[47] An example of a drug that directly acting on DNA methylation is hydralazine. It is an antihypertensive drug which inhibits DNA methylation. Isotretinoin is an indirectly affecting drug with transcription factor activity. It can be explained through a two-tier mechanism in which acute exposure to a drug affect signaling pathways which alter transcription factor activity at the region of gene promoters. This events result an altered expression of genes which code for receptors, signaling molecules, and other proteins involved in alteration of genetic regulatory circuits. Chronic exposure to a drug causes adaptation of cells to afore described process that ultimately results in permanent alterations to chromatin structure and DNA methylation which leads to permanent modifications of a given epigenetic network. Hence, any epigenetic side-effect resulted from a drug may carry on even after the discontinuation of the drug.[47]

2.4 Pharmacogenetic testing

Pharmacogenetic testing refers to a genetic test that predicts the patient's likelihood of experiencing an adverse effect or not as a response to a given drug. Pharmacogenetic testing may enable clinicians to identify those patients who are less likely to benefit from expensive drugs, and those who are susceptible to severe treatment-related toxicities at standard treatment doses, thus making treatments safer and more cost-effective. The availability of high-throughput genotyping platforms has allowed a large set of SNP markers to be studied and may lower the cost of pharmacogenetic testing.[27,28] Owing to the importance of genetic variations on drug response, increasing capacities and decreasing costs of next-generation sequencing (NGS) platforms have facilitated large-scale studies of genetic variation. In addition, NGS assays are becoming increasingly implemented in clinical diagnostics.[29,30] NGS-based analysis indicates that over 90% of the overall genetic variability in pharmacogenes is brought up by rare genetic variants, however, the impact of rare genetic variations on drug pharmacokinetics has not been systematically reviewed yet.

Individual differences in drug efficacy, or susceptibility to adverse effects, collectively make an important contribution to the burden of ill-health. Studying the genetic basis of this differentiation can be performed by clarifying pathways and mechanisms of drug action or metabolism and development of genotype based predictive tests of efficacy or toxicity.[31] According to the research in common disease susceptibility, the path to translation involves a two-stage process; identification of the genetic loci involved, and then performing research into the healthcare applications of this knowledge, which in turn link with critical evaluation of the determination of genotype as a predictive test. While the extent of the clinical impact of research in both areas is indeterminate, the accurate identification of loci involved in drug response appears to be less advanced than the identifying susceptibility loci for common disease.[32] After more than two decades of research, a continuing expansion in the range and depth of available drug therapies, and the continued promise of 'personalized medicine' only four pharmacogenetic tests were mandated as part of the FDA drug approval pre-July 2009, while for another 10 tests recommended by the FDA, clinical utility is not universally agreed.[33,34] Understanding the reasons for the blocks in development of personalized medicines could help improve efficiency of future research. Systematic reviews and field synopses have previously exposed to the obstacles to progress in complex disease genetics such as targeting on candidate genes rather than performing genome-wide analysis; inadequate sample size; suboptimal capture of genetic variability; and significance of chasing and reporting bias. All of these led to a failure in replicating and validating genetic associations.[35] These overviews were followed by improvements in research design, which made an important contribution to the recent success in the identification in genes for common disease.[36] These considerations and the absence of a prior systematic, quantitative overview of pharmacogenetic research was the motivation for this systematic review.

In oncology, pharmacogenetics is the study of analyzing germline mutations (e.g., SNPs affecting genes coding

for liver enzymes which is responsible for drug deposition and pharmacokinetics), whereas pharmacogenomics refers to analyzing somatic mutations in tumoral DNA leading to altered drug response (e.g., KRAS mutations in patients treated with anti-Her1 antibodies).[37] Pharmacogenetics is believed to account for inter-ethnic differences (e.g., between patients of Asian, Caucasian and African descent) in adverse events and efficacy profiles of many widely used anticancer drugs in chemotherapy.[38,39,40]

The incidence of population discrepancies in response to such drugs and the series of adverse drug reactions (ADRs) are arisen as a general phenomenon. Moreover, ADRs owe a massive public health issue due to exacerbation of patient's ill condition and additional cost for ADR-related hospitalizations. For an example, the cost of ADR-related hospitalization accounts for $136 billion in the USA alone during past few years.[48]

Population differences in drug response directly impact on the process of drug development specially in performing clinical trials of diverse ethnicities. However, most of the clinical trials are still carried out only in developed countries.[47,48] Obviously, such an approach towards drug development will enhance the risk for unexpected drug-related toxic reactions in other populations. The high cost for carrying out clinical trials in different ethnic populations from different regions in the world create greater economic burden for drug developing companies. As it will enhance the cost of drug development, patients will also have to bear a high cost. Furthermore, such meticulous trials will also reduce the chance to succeed the marketing of beneficial drugs that due to incidence of ADR in one or more populations. The prediction of potential differences in diverse populations for drug response at the preliminary stage of drug development could be a one solution to avoid said issues.[48,49] Another possible clinical solution is classifying population groups that are prone to be produced potential ADR. It helps the drug developer to get rid of costly clinical trials. In addition, this approach accelerates the process of entry of potentially beneficial drugs to the drug market for the right group of people.[48,49]

Generally, world population can be classified in to three major groups that exhibit differences for drug response namely population of European descent, population of African-American and East Asian descent. Since major clinical trials are primarily conducted for the European population or American population, ADR in drug response are reported after marketed the new drug to other world populations. For an example, 5-Fluorouracil is a commonly used anti-cancer drug which reported differences in ADR in drug response among different groups of world population. Hematologic toxicity including leukopenia and anemia is the major side effect associated with 5-Fluorouracil. These differences are due to varied activity of the enzyme dihydropyrimidine dehydrogenase, in some individuals, dihydropyrimidine dehydrogenase enzyme is deficient which is more prone to 5-fluorouracil-induced hematologic toxicities.[49,50]

Warfarin is a widely used anticoagulant drug for the prevention of thrombosis and embolism that also exhibits significant differences in drug response among different nations. In spite of its effectiveness, warfarin treatment needs fine-tuning to make sure an adequate and safe dose to give the patient, otherwise the patients are at high risk condition of bleeding or warfarin dose may be inadequate to shield the patient from thromboembolism. Ethnic differences seen in the warfarin dose is an important factor to consider for an effective treatment and it has been well documented although not frequently esteemed by the clinicians.[50]

3. CONCLUSIONS

The genetic and molecular basis of personalized medicine display firm evidences to emerge its budding importance in medical care. Incorporating pharmacogenetic testing in early clinical trials may provide vital information about pharmacogenetic profiles with treatment responses and tolerability. This information can help investigators identify patients with specific pharmacogenetic profiles, and may reduce the size and cost of phase III clinical trials needed to establish drug efficacy. In summary, expansion in knowledge and research on pharmacogenomics has made out a direct impact on drug development, clinical trials and clinical practice.

Since the MDR1 gene and P-gp were proved to induce drug resistance in certain tumors, pharmacogenetics concepts have had a significant impact on individual response of drugs treatment and genotyping has been considered a new tool for predicting individual drug-metabolizing capabilities and therapeutic establishment. The utility of pharmacogenetics extends beyond cancer therapy. It has the potential to facilitate the identification of drug targets and accelerate drug discovery and development.

Ethnic differences in different populations of the world are an important fact to consider in carrying out clinical trials for new drugs and deciding the dosage of the respective drug. Yet there is no efficient process to perform clinical trials as cover the different nations in different regions of the world. This review emphasizes the drawbacks that are frequently found in the field of Pharmacogenomics.

4. Conflicts of Interest

The authors declare that they have no conflicts of interests.

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