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# Insights and Current Perspectives on Pharmacogenomics of Antimalarial Drugs

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## ABSTRACT

Malaria constitutes a major public health concern in tropical and other malaria-endemic regions. Genetic and non-genetic factors are known to influence the pharmacokinetics and/or pharmacodynamics of drugs including antimalarial drugs resulting in variability in drug responses. This article aimed to update perspectives on pharmacogenomics and also provide an updated appraisal of genetic variability in drug-metabolizing enzymes which alter the disposition of antimalarial drugs causing variations in treatment outcomes. Important literature databases such as Elsevier, IEEExplore, Pubmed, Scopus, Web of Science, Google Scholar, ProQuest, ScienceDirect, and BioMed Central were selected based on the quality, extant content, and broad area of the discipline. The specific keywords related to the study were identified and used for the study purposely to identify related works. Advances in genetic research have facilitated the identification of Single Nucleotide Polymorphisms (SNPs) that alter the activity of drug-metabolizing enzymes that metabolize most antimalarial drugs**.** There is an association between isoforms of CYP450 gene variants and the efficacy of some antimalarial drugs, and this may be applied to the optimization of malarial therapy. Although identification of cytochrome P450 (CYP450) gene variants can be used for personalization of malaria treatment, several challenges are encountered in this process but some resources provide education and guidelines on how to use the pharmacogenetic results of specific drugs.

**Keywords:** Antimalarial drugs; Cytochrome P450; Gene Variants; Pharmacogenomics

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## INTRODUCTION

Malaria, mostly caused by *Plasmodium falciparum*, continues to be a major public health problem in tropical and other malaria-endemic regions. The latest report by the World Health Organization (WHO) indicates that there were about 241 million malaria cases and about 627,000 malaria deaths in 2020, with the WHO African Region accounting for about 95% of this malaria cases [1]. The emergence of antimalarial drug resistance challenges the control and treatment of malaria, necessitating regular monitoring of drug efficacy [2]. The current mainstay and first-line treatment for the majority of cases of malaria is artemisinin-based combination therapy (ACT) in which a rapid-acting with short half-life artemisinin or its derivative is combined with a drug with a longer half-life [1]. Another strategy aimed at enhancing the effectiveness of antimalarial treatment is the application of findings on Pharmacogenetics/pharmacogenomics of antimalarial drugs.

Pharmacogenetics involves the study of how inter-individual differences in a single gene can affect an individual's response to particular drugs, while the term pharmacogenomics is much broader and it involves investigating the entire genome to assess their effects on drug responses. Pharmacogenetics/pharmacogenomics This field of study aims at developing effective and safe medications with doses that are tailored to variations in a person's genes [3,4]. Plasma drug levels have been reported to vary as much as 1000-fold when the same drug dose is administered to different individuals with the same body weights, and this is due to variations in genes encoding cytochrome P450 (CYP450) and other Drug metabolizing enzymes [5].

It has been established that there are more than 14 million Single Nucleotide Polymorphisms (SNPs) in the entire human genome, and these variations in the human genome occur approximately in every 300–1000 nucleotides [6]. Most SNPs are attributable to independent single mutational events in the past [7]. Thus, where there are inter-individual variations in drug responses, the identification of a variant of the gene that mediates the variation would lead to optimization of the treatment efficacy and reduction of the adverse effect profiles of drugs in a given population [8]. However, it is known that apart from genetic factors, other factors can influence the outcome of drug therapy and these include environmental factors (exposure to some chemicals in the environment), physiological factors (age, sex, hepatic and renal functions, pregnancy), lifestyle factors (smoking, drinking alcohol, exercise) and concomitant drug use [9,10]. Pharmacogenomics is a part of personalized medicine or precision medicine that individualizes therapy by using SNPs and tailor-making medicines to each patient for effective therapy [11]. We have carried out numerous studies in our laboratories on pharmacokinetics and pharmacogenomics of different antimalarial drugs and diverse anti-infective agents to generate data for optimization of the drug efficacies [12-14].

An earlier review on the pharmacogenetics of antimalarial drugs by Kerb and co-workers was reported when, as acknowledged by the authors, pharmacogenetic research into antimalarial drugs was still in its infancy [15]. Within more than 12 years since the publication of this review article [15], a deluge of publications have appeared in the literature on pharmacogenetic studies into antimalarial drugs. A later review article by Elewa and Wilby on pharmacogenetics of antimalarial drugs reported only on pharmacogenetic studies in malarial patients with associated clinical outcomes [16] Thus, only a few studies (about 10) met the inclusion criteria and this limited the coverage of studies on the pharmacogenetics of diverse antimalarial drugs. We found it necessary to present an updated report on current perspectives on pharmacogenomics in general, and also provide up-to-date insights into polymorphisms within the genes encoding for drug-metabolizing enzymes which alter the pharmacokinetics of antimalarial drugs, with the potential to cause variations in antimalarial drug responses.

## MATERIALS AND METHOD

### Review Strategy and study selection

This review is designed to study the insights and current perspectives of pharmacogenomics of antimalarial drugs. It identifies the dominant roles of pharmacogenomics in antimalarial drugs. Studies show that unstructured literature review (ULR) has been popularized in medical studies.

As a result, ULR as a method is adopted in this study to summarize research findings (Figure 1).

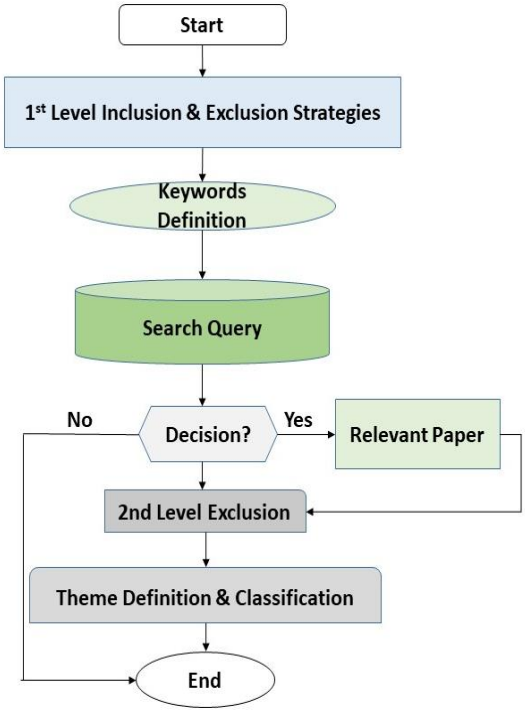


**Figure 1: Study Selection Scheme**

Key literature databases were selected based on the quality, extant content, and broad area of the discipline. These include Elsevier, IEEExplore, Pubmed, Scopus, Web of Science, Google Scholar, ProQuest, ScienceDirect, and BioMed Central. The keywords related to the study were identified and used for the study, purposedly to identify related works. These are "antimalarial drugs", "personalized medicine", "pharmacogenomics", "pharmacogenetics", "metabolism", "cytochromes", "amodiaquine", "artesunate", "artemisinin" "artemether", "chloroquine", "chlorproguanil", "lumefantrine", "mefloquine" "piperaquine", "primaquine", "proguanil", "pyronaridine", "quinine", "tafenoquine". These keywords were explicitly used to search in the selected database.

**Data extraction**

To identify eligible papers, 6 criteria were put in place:

1. The paper must be peer-reviewed.
2. Must be written in the English language.
3. The paper must be in the pharmacogenomics/pharmacogenetics discipline.
4. The paper is investigating the pharmacogenomics of antimalarial drugs
5. The paper described the metabolism of antimalarial drugs.
6. The paper identified at least one cytochrome P450 metabolizing enzyme.

Before accepting any of the papers for investigation, further screening was performed using these conditions:

1. The Paper is not available for download.
2. The Paper's findings are a repetition of an earlier reviewed work.
3. An extended journal paper from a conference is preferred to the conference paper.

After performing the search query, each paper's abstract and keywords were manually sieved to exclude papers not related to the study.

## RESULTS AND DISCUSSION

**Evolution of Pharmacogenetics and Genes of Importance**

The concept of pharmacogenetics/pharmacogenomics has been evolving along with remarkable strides made in the completion of the map of human genome sequence by the International Human Genome Sequencing Consortium [17,18]. Following the completion of the human genome project in the 2000s, numerous researchers have gone into studying the impact of genetic variation, especially SNPs, on drug response. The current status of pharmacogenetics development can be seen at PharmGKB website https://www.pgrn.org/pharmgkb.html developed by the US-based Pharmacogenomics Research Network (PGRN) that provides general information on individual polymorphisms and the impact of pharmacogenetics on response to specific drugs [19]. PharmGKB collates

drug dosing guidelines based on variations in pharmacogenetics which are published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), and other Pharmacogenetics Working Groups in different countries. With the availability of more validated scientific reports and data, drug regulatory agencies of several countries have listed hundreds of drugs requiring the determination of genomic biomarkers for optimization of drug efficacy and safety through dosage adjustment [20].

Cytochrome P450s (CYP450s), a superfamily of haemoproteins, play a very important role in phase I drug metabolism as they are known to metabolize about 80 to 90% of clinically used drugs [21]. The CYP450 isoforms that are very important in human drug metabolism include CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (Figure 2), and are each encoded by different genes [19,22]. Alterations in enzyme function such as increased or decreased activity result from mutations in a CYP gene that encodes for the enzyme. A mutant allele that occurs at a frequency of not less than one percent in a population is recognized as a pharmacogenetic polymorphism. Generally, polymorphisms can be identified in a population through genetic studies (identifying the mutant allele) and/or through determining altered enzyme function (ie phenotype studies) [23]. In terms of the extent of variations in drug metabolism in different ethnic groups and the number of drugs that are metabolized by each CYP450, it has been shown that the most important polymorphic CYPs are 1A2, 2C9, 2C19, and 2D6 [23]. However, widespread polymorphisms have also been observed in other CYP genes, such as CYP1A1, 2A6, 2C8, 3A4, and 3A5 [24]. Pharmacogenetic studies have shown that individuals can be classified into one of four general metabolizer types - Poor Metabolizer (PM), Intermediate Metabolizer (IM), Extensive Metabolizer (EM) and Ultra-rapid Metabolizer (UM). In the poor metabolizer group, the enzyme activity is abolished because they have a gene variant in which there are two nonfunctional alleles or the entire gene is deleted such that adverse drug effects at standard doses may be experienced due to drug accumulation. An intermediate metabolizer phenotype has decreased enzyme activity and is usually found in individuals carrying one nonfunctional allele and another allele with reduced function. The extensive metabolizer (now called normal metabolizer) phenotype is characterized by normal enzyme activity because one or two alleles have normal function, while the Ultra-rapid Metabolizer has increased enzyme activity as they carry more than one extra functional gene [25]. The variant alleles of CYP genes are distributed differently among different ethnic populations [25].

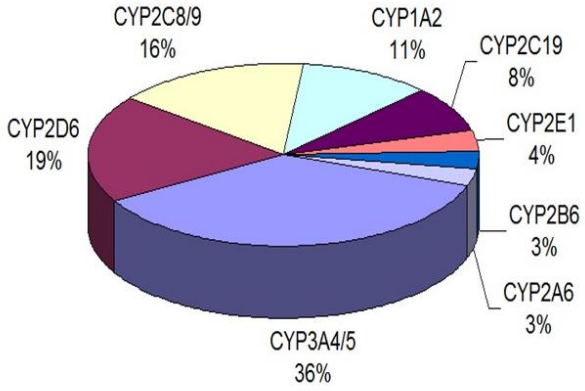


**Figure 2: Proportion of Drugs Metabolized by CYP450 Isoenzymes 22**

The enzymes involved in Phase II biotransformation also have isoforms that exhibit genetic polymorphisms which can influence the outcome of drug therapy. Generally, there are fewer instances in which drug clearance is influenced by variations in the genes that encode for the phase II enzymes because phase I metabolic reactions are usually the rate-limiting steps in the overall drug pharmacokinetic process [19].

It is pertinent to note that genetic variations resulting in inter-individual drug responses are not only due to the presence of variants of genes encoding drug-metabolizing enzymes, genetic variation in drug transporters and drug targets (e.g., receptors) can also have a great effect on drug efficacy, with several examples already identified [26].

**Impact of Pharmacogenetics on Antimalarial Treatment Efficacy**

Pre-emptive genotyping of actionable genetic variants could be a good tool to optimize pharmacotherapy in patients [8]. The impact of genetic variants on antimalarial drugs and their clinical implications are outlined below and summarized in Table 1.

**Amodiaquine**

Amodiaquine, a 4-aminoquinoline (Figure 3), is rapidly metabolized by CYP2C8 to N-desethylamodiaquine (DEAQ) which is 3-times less active than the parent drug but has a slower rate of elimination [27]. The CYP2C8 gene has primarily two major alleles, *CYP2C8*2* and CYP2C**3*, and both are associated with slow metabolizer phenotype, with **3* identified to result in significantly impaired metabolism. The prevalence of CYP2C8 gene varies in different ethnic populations as shown in Table 1 [28,29]. A recent study has shown that *CYP2C8*2* and **3* frequencies among Eritreans are intermediate between the values documented for Caucasians and Africans [30]. Studies have been undertaken to determine whether the efficacy of amodiaquine is affected by *CYP2C8* polymorphisms. It has been shown that treatment outcomes with amodiaquine do not vary with the CYP2C8 genetic variants, but there was an increased risk of non-serious adverse events in CYP2C8*2 or CYP2C8*3 allele carriers compared to the wild-type [27,28,31].

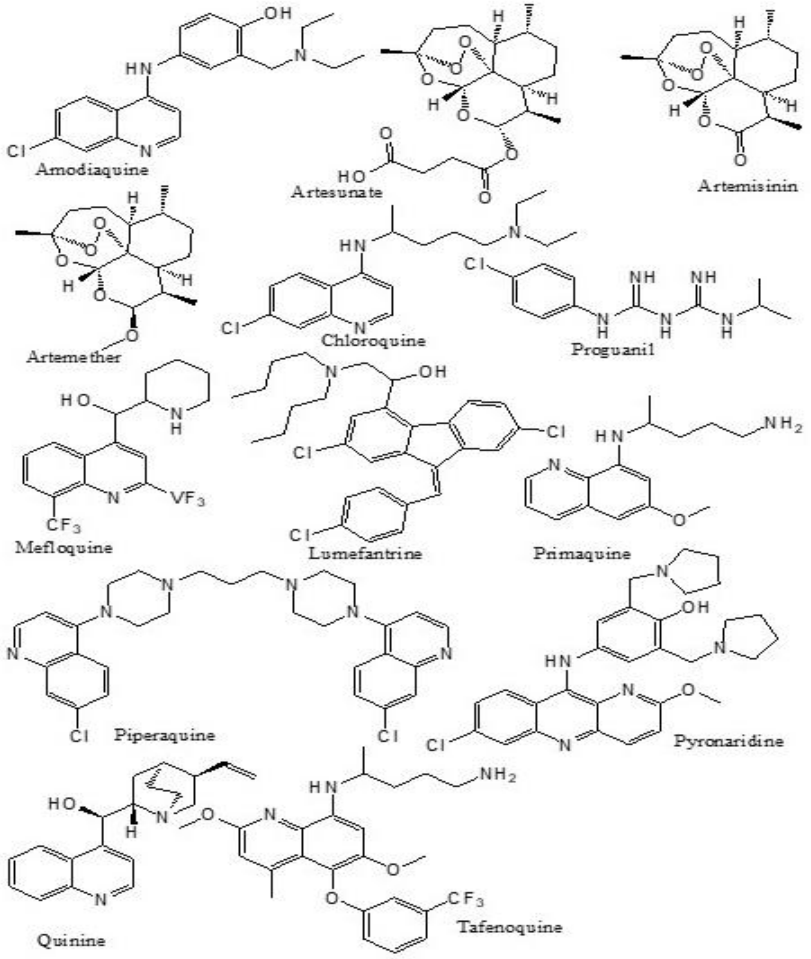


**Figure 3: Chemical Structures of Antimalarial Drugs**

**Artesunate**

Artesunate, a sesquiterpene lactone derivative (Figure 3), is metabolized to an active dihydroartemisinin (DHA) primarily by CYP2A6 [32]. The *CYP2A6* gene is reported to be highly polymorphic, with over 35 different CYP2A6 alleles described and the majority of them have been shown to alter CYP2A6 enzyme activity. The most common of these CYP2A6 variant alleles include CYP2A6*1B, CYP2A6*2, CYP2A6*4, CYP2A6*7, CYP2A6*9 and CYP2A6*10 [32]. Across ancestral groups, a wide variation in the frequency of CYP2A6 alleles is observed, as summarized in Table 1 [15,33,34]. A study assessing the influence of CYP2A6 gene on the incidence of adverse effects in healthy Malaysian volunteers receiving single doses of artesunate with amodiaquine showed that significantly more adverse effects were noted in those patients with CYP2A6*1B variant (UM phenotype) which may be due to accumulation of the active metabolite, dihydroartemisinin [35]. People with poor metabolizer phenotypes of CYP2A6 have higher concentrations of artesunate and lower concentrations of DHA. This may reduce the drug's antimalarial activity since artesunate has higher intrinsic antimalarial activity compared to DHA. However, this has not been documented.

**Table 1: Antimalarial drugs and associated CYP450 Enzyme variants with Phenotype frequencies in different ethnic populations**

| Antimalarial Drug/Enzyme Variants | Phenotype | Phenotype Frequency in Africans (%) | Phenotype Frequency in Caucasians (%) | Phenotype Frequency in Asians (%) | Clinical Implication |
|---|---|---|---|---|---|
| **Amodiaquine, Chloroquine** | | | | | **Amodiaquine:** Treatment outcomes with amodiaquine do not vary with the CYP2C8 genetic variants. There is increased risk of amodiaquine related ADR in PM<br>**Chloroquine**: Wild-type CYP2C8 individuals achieved greater reduction of gametocytes than PM |
| CYP2C8*2 | PM | 11 -22 | <1 | 0 | |
| CYP2C8*3 | PM | 0 – 2.1 | 15 | <0.1 | |
| **Artesunate** | | | | | |
| CYP2A6*1B | UM | 11 - 18 | 28 - 35 | 26 - 57 | Increased adverse effect due to accumulation of active metabolite in UM |
| CYP2A6*2 | PM | 0-1 | 1-5 | 0 | |
| CYP2A6*4 | PM | 0.5-3 | 0.1-4 | 5-24 | Possible reduction in antimalarial activity in PM |
| CYP2A6*7 | PM | 0 | 0-3 | 2-13 | |
| CYP2A6*9 | PM | 6-10 | 5-8 | 16-22 | |
| CYPA6*10 | PM | 0 | 0 | 0.4-4 | |
| **Artemisinin, Artemether** | | | | | **Artemisinin**: No documented association of CYP2B6 variants with drug efficacy<br>**Artemether:** *CYP2B6* and *CYP3A4/5* polymorphisms have no obvious effects on artemether treatment outcome |
| CYP2B6*4 | UM | 0 | 4 - 6 | 3 - 40 | |
| CYP2B6*6 | PM | 25 – 50 | 15 – 25 | 12 - 19 | |
| CYP2B6*9 | PM | 20 - 50 | 2 – 29 | 2 - 47 | |
| CYP2B6*18 | PM | 2 - 8 | 0 | 0 | |
| **Proguanil, Chlorproguanil** | | | | | Treatment failure may or may not be associated with decreased formation of cycloguanil in PM phenotypes. Further studies are required to clarify the clinical significance of *CYP2C19* polymorphism in Proguanil efficacy |
| CYP2C19*2 | PM | 15 – 25 | 12 | 29 – 35 | |
| CYP2C19*3 | PM | 0-1 | <1 | 2 - 9 | |
| CYP2C19*17 | UM | 16 | 21 | 3 | |
| **Mefloquine, Artemether, Lumefantrine, Piperaquine, Quinine** | | | | | |
| CYP3A5*3 | PM | 12 – 40 | 82 - 95 | 40 – 80 | **Mefloquine:** ABCB1 (TT) variant were found to have a three-times greater chance of successful treatment outcome compared with other genotypes (CC and CT).<br>**Lumefantrine**: Most studies demonstrated that *CYP3A4 and CYP3A5* gene |
| CYP3A5*6 | PM | 7-17 | 0 | 0 | |
| CYP3A5*7 | PM | 10 | 0 | 0 | |
| CYP3A4*1B | EM | 77 | 2.7 | 11 | |

| | | | | | |
|---|---|---|---|---|---|
| CYP3A4*1G | EM | 85 | 8.2 | 40 | variants showed no relationship with pharmacokinetic profiles of lumefantrine or treatment outcomes. **Piperaquine:** CYP450 genetic variants were found to have no significant effect piperaquine elimination. **Quinine**: There is a significant influence of few CYP3A5 variant alleles (CYP3A5*3,*4,*6, *7, and *9) on quinine metabolism |
| CYP3A4*22 | PM | 0.08 | 5 | 2.6 | |
| **Primaquine, Tafenoquine** | | | | | |
| CYP2D6*1xN | UM | 0 -1 | 0 – 3 | 0 – 3 | **Primaquine**: PM phenotypes of CYP2D6 variants have been shown to lead to therapeutic failure with primaquine. **Tafenoquine**: No association of CYP2D6 polymorphism with tafenoquine efficacy has been observed |
| CYP2D6*2xN | UM | 1-2 | 0-3 | 0-1 | |
| CYP2D6*2 | PM | 14-19 | 20-25 | 13-29 | |
| CYP2D6*4 | PM | 3-6 | 10-18 | 1-12 | |
| CYP2D6*5 | PM | 4-5 | 1-3 | 1-4 | |
| CYP2D6*10 | PM | 3-7 | 2-5 | 1-10 | |
| CYP2D6*17 | PM | 17-20 | 0-1 | 0-2 | |
| CYP2D6*41 | PM | 6-12 | 8-17 | 2-13 | |

**Artemisinin**

The CYP450 isoform that mainly mediates the metabolism of artemisinin, a sesquiterpene lactone (Figure 3), is CYP2B6, with a contribution by CYP3A4 resulting in the formation of an active metabolite, dihydroartemisinin (DHA) [36]. Currently, more than 100 described SNPs of the *CYP2B6* genes have been reported and the major CYP2B6 variants are CYP2B6*4, CYP2B6*6, CYP2B6*9, and CYP2B6*18 [36]. The *CYP2B6*6* and CYP2CB6*9 are the most common allele and occur in up to over 50% of different populations. CYP2B6*4 which codes for Ultrarapid metabolizer phenotype is rare in Africans compared to Caucasians or Asians. On the other hand, CYP2B6*18 is more frequent in Africans and rare in Caucasians and Asians (Table 1) [37]. While the UM phenotypes have reduced drug exposure, the PM variants are associated with increased plasma concentrations of artemisinin [29,36]. However, no studies have reported an association between the CYP2B6 gene variants and artemisinin efficacy.

**Artemether**

Artemether, a derivative of artemisinin (Figure 3), undergoes rapid and extensive demethylated to the biologically active main metabolite DHA through CYP3A4/5 and CYP2B6. While the liver CYP3A4 is not important in the *in vivo* metabolism of artemether, this CYP450 isozyme plays a role in the pre-systemic metabolism of the drug [14].

To date, no studies have been published on artemether monotherapy pharmacogenetics. The few available reports concern Artemether-lumefantrine. The association of CYP2B6*6 genotype with artemether disposition was demonstrated in a decreased metabolism of artemether in CYP2B6*6 volunteers (PM) and the authors concluded this is unlikely to result in differences in artemether-lumefantrine efficacy and treatment outcomes [14].

In a study that assessed the effects of CYP2B6 and CYP3A4/5 polymorphisms on artemether disposition, no associations were found between artemether elimination and *CYP2B6*6,* CYP3A4*1B and CYP3A5*3 alleles carriers [38]. Hence, CYP450 genetic variants may not influence artemether treatment outcome.

**Chloroquine**

The metabolism of Chloroquine, a 4-aminoquinoline (Figure 3), is mediated mainly by CYP2C8 and to a lesser degree by CYP3A4 and CYP2D6 to an active metabolite (N-desethylchloroquine) in addition to other minor metabolites [39]. The frequencies of the CYP2C8 variants in different populations are depicted in Table 1 [37]. In malaria treatment/prophylaxis studies with chloroquine, a 2.5- to 5.6-fold inter individual variability in CQ concentrations has been reported and this may affect treatment outcome. A study has shown that in chloroquine/primaquine treated patients, there is a relationship between CYP2C8 allele variants and gametocytemia and parasitemia clearance rates. Wild-type

individuals achieved a greater reduction of gametocytes than low-activity alleles of CYP2C8 (i.e., *2, *3, and *4) carriers. The results suggested that CYP2C8, CYP2C9 and CYP23A5 genetic variants may influence chloroquine pharmacokinetics thereby affecting treatment outcome [40].

**Chlorproguanil and proguanil**

The biguanide derivatives, chlorproguanil and proguanil (Figure 3) are bioactivated to chlorcycloguanil and cycloguanil, respectively, by CYP2C19 and, to a lesser extent, by CYP3A4 [15]. The frequency of the CYP2C19 alleles varies considerably among different ethnic populations (Table 1). The two variant alleles, CYP2C19*2 and CYP2C19*3, are largely associated with the PM phenotype while CYP2C19*17 allele results in increased CYP2C19 expression and activity. The CYP2C19*2 is the most common CYP2C19 variant among the various populations, while *CYP2C19*3* allele frequencies in most populations is below 1% but more prevalent among Asians [28,37]. Although a study on malaria prophylaxis with proguanil in Tanzanians showed that treatment failure was associated with decreased metabolism of the drug in PM phenotypes, other studies demonstrated that the therapeutic efficacy of proguanil was comparable between the PM and EM patients even when the extent of metabolism differed significantly between the two groups [28]. Further studies are required to clearly understand the clinical significance of CYP2C19 polymorphism in the efficacy of proguanil/cycloguanil.

**Lumefantrine**

Lumefantrine which belongs to the group of arylamine alcohols like halofantrine (Figure 3) is used together with artemether in artemisinin-based combination therapy (ACT). This highly lipophilic drug is primarily metabolized by CYP3A4/CYP3A5 to a metabolite, desbutyl-lumefantrine which has a significantly higher antimalarial activity than the parent drug, ($IC_{50}$ 4–5-fold higher) [41]. Both CYP3A4 and 3A5 have overlapping substrate specificities. The CYP3A5 gene has three major alleles that have been well studied (CYP3A5*3, CYP3A5*6 and CYP3A5*7) and they are associated with slow metabolizer phenotypes. Their frequencies vary considerably among different ethnic populations (Table 1) [32]. The most studied variants of CYP3A4 that occur in high frequencies include, CYP3A4*1B, CYP3A4*1G, and CYP3A4*22 (Table 1). Several studies have investigated whether the CYP3A4 variants result in significant differences in blood levels of lumefantrine. These studies demonstrated that the major CYP3A4 and CYP3A5 gene variants showed no relationship with pharmacokinetic profiles of lumefantrine or treatment outcomes [38,43]. On the other hand, another study reported that CYP3A5*3 genetic variant was associated with only a high maximum plasma concentration of lumefantrine [44]. Thus, further investigations are

required to clarify the association between CYP3A5*3 gene variants, lumefantrine pharmacokinetics and therapeutic efficacy.

**Mefloquine**

Mefloquine, a 4-quinoline derivative (Figure 3), is metabolised by CYP3A4/CYP3A5 to two major pharmacologically inactive metabolites, carboxymefloquine and hydroxymefloquine [33]. The variants of CYP3A4 and CYP3A5 genes and the frequencies of occurrence in different ethnic populations are presented in Table 1. Pharmacogenetic studies of mefloquine are mostly on genetic polymorphisms of the major genes encoding drug efflux transporters - ABCB1, ABCG2, and ABCC1. While no significant association was found between the ABCG2 and ABCC1 gene polymorphisms and mefloquine treatment outcome, patients carrying the ABCB1 (TT) variant were found to have a three-times greater chance of successful treatment compared with other genotypes (CC and CT). Thus, predicting responses to artesunate-mefloquine treatment can be based on using ABCB1 polymorphisms as useful genetic markers [45].

**Primaquine**

Primaquine, an 8-aminoquinoline (Figure 3) has been an antimalarial drug of choice in the treatment of *Plasmodium vivax* and *Plasmodium ovale* hypnozoites, and for malaria prophylaxis. It is metabolized principally by CYP2D6 isoenzyme to active metabolites, 5-hydroxy derivative of primaquine, that are responsible for the pharmacological effect of primaquine [12]. CYP2D6 gene is highly polymorphic with over 90 known allelic variants, demonstrating significant inter-individual and inter-ethnic differences in its activity (Table 1) [37,46]. Some of these CYP2D6 variants with a prevalence of >1% in different ethnic groups are shown in Table 1 Most of them are PM except CYP2D6*1xN and CYP2D6*2xN variants that are Ultra-rapid metabolizer phenotypes (Table 1), Recent studies have shown an association of polymorphisms related to CYP2D6 activity and treatment outcome with primaquine. PM phenotypes of CYP2D6 variants have been shown to lead to therapeutic failure with primaquine [46].

**Piperaquine**

Piperaquine, a bisquinoline (Figure 3), had been extensively used as a monotherapy but it is now commonly used as a partner drug with dihydroartemisinin in the ACT. Piperaquine is metabolized primarily by CYP3A4 and CYP3A5 into two major metabolites, piperaquine *N*-oxide and piperaquine *N*, *N*-dioxide, and both metabolites are biologically active contributing to the efficacy of piperaquine [47]. The variants of CYP3A4 and CYP3A5 genes and their occurrence frequencies are shown in Table 1. There is a paucity of studies on the pharmacogenetics of piperaquine. In studying the effect of SNPs in Cytochrome P450

isoenzyme genes on the metabolism of Artemisinin-Based Combination therapies, genetic variants were found to have no significant effect on piperaquine elimination [38].

**Pyronaridine*e***

Pyronaridine, benzonaphthyridine derivative (Figure 3**),** had previously been used in the treatment of malaria as a single agent, but it is currently used in combination with artesunate, representing a second-generation ACT. The metabolism of pyronaridine is mediated by multiple and varied pathways and studies with recombinant human CYP450 isoforms indicated that pyronaridine could be metabolized by CYP1A2, CYP2D6 and CYP3A4, generating nine metabolites [48]. The literature is deficient in studies on the investigation of a possible association of genes of CYP450 isoforms and pharmacokinetics or therapeutic efficacy of pyronaridine. Pyronaridine has a low metabolic turnover, thus pharmacogenetic studies of the drug might not be of significant value [48]. Pyronaridine is a P-glycoprotein substrate and may exhibit variable oral absorption based on its significant P-gp-mediated efflux [49]. It has been postulated that due to the importance of this transport protein in the processes of oral absorption for a range of susceptible drugs, the polymorphism of P-gp gene might be able to affect the oral absorption of pyronaridine

**Quinine**

Quinine is metabolised by CYP3A4/3A5 to its main metabolite, 3-hydroxyquinine, which contributes up to 10% of the antimalarial activity of the parent compound [25]. In vitro study on the effects of different CYP3A4 allelic variants on intrinsic clearance towards quinine revealed that most of the variants had significantly reduced activity while 2 variants showed increased activity and 2 other variants had no significant differences in quinine metabolism, compared with a wild-type allele, CYP3A4*1A [25]. These results suggest that if these *in vitro* findings are replicated *in vivo,* patients that are carriers of these alleles with reduced intrinsic clearance of quinine may potentially be CYP3A4 poor metabolizers and may therefore be more prone to adverse reactions of the quinine and also require lower doses of the drug to achieve therapeutic efficacy. Pharmacogenetic studies in Tanzanian and Ugandan populations demonstrated a significant influence of a few CYP3A5 variant alleles (CYP3A5*3,*4,*6, *7, and *9) on quinine metabolism [50,51]. Considering that quinine is an antimalarial drug with a narrow therapeutic window and concentration-dependent serious adverse reactions, these findings suggest that CYP3A4/5 allelic variants with PM phenotypes can be associated with adverse reactions of antimalarial therapy with quinine.

**Tafenoquine**

Tafenoquine, a new 8-aminoquinoline drug (a primaquine analogue) with long half-life was approved for use in the chemoprophylaxis and treatment of malaria. Similar to primaquine, the metabolism of tafenoquine is principally mediated by CYP2D6 but clinical studies have

not identified an association of CYP2D6 polymorphism with tafenoquine efficacy [52]. Thus, the efficacy did not appear to be reduced in poor or intermediate metabolizers of CYP2D6.

**Clinical Implication and Challenges of Pharmacogenomics Testing**

The integration of pharmacogenetic testing into clinical practice has been evolving over the years, Currently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and other related pharmacogenomics research organizations have provided specific pharmacogenetic guidelines on how to use pharmacogenetic information relating to some drugs. Pharmacogenetics/pharmacogenomics testing is required especially for some classes of drugs that are metabolized by one or more variant alleles of the Cytochrome P450 enzymes, and drugs with a narrow therapeutic window [53]. Interpretation of pharmacogenetics test results for pro-drugs is different from those of active parent drugs. For example, while poor metabolizers of active parent drugs have high plasma drug levels that may result in toxicity, the same phenotype taking a pro-drug will have a therapeutic failure because its metabolite which is the active moiety is not produced. A typical example is primaquine where CYP2D6 PM phenotypes have treatment failures. The corollary is that while ultrarapid metabolizers of active parent drugs may have reduced drug response due to rapid drug clearance, the same phenotype taking a pro-drug will manifest increased drug response following efficient generation of the metabolites which have therapeutic activity [54]. There are currently about 400 medicines with FDA-approved information on pharmacogenetic product labels but only three antimalarial drugs (chloroquine, primaquine and quinine) are currently contained in the list [55]. However, PharmGKB has Drug label annotations containing pharmacogenetic information for over 800 drugs which include most of the antimalarial drugs such as lumefantrine, artesunate, chloproguanil, dapsone, tefanoquine, artemether, proguanil, and mefloquine (http://www.pgrn.org/pharmgkb.html) [56].

Many challenges have been encountered in the implementation of pharmacogenetics in a clinical setting. Some of these challenges include:

1. Most healthcare providers do not have a clear understanding of the applicability of pharmacogenetic tests. Drug dosage adjustment based on non-genetic parameters like age, body weight, and hepatic and renal function tests is well understood and practiced. Some resources have addressed this lacuna and these include the Clinical Pharmacogenetics Implementation Consortium (CPIC; https://cpicpgx.org/) Other resources are: My Drug Genome (https://www.mydruggenome.org); IGNITE (https://www.gmkb.org); GTR (https://www.ncbi.nlm.nih.gov/gtr); eMERGE (https://www.emerge-network.org) and Coursera (https://www.coursera.org/learn/personalizedmed) [57].

2. Even when the clinical utility of pharmacogenetics tests is appreciated, some clinicians can encounter difficulties in the interpretation of the pharmacogenetic test results to apply them to patient care. Again, there are several resources available for the relevant knowledge and necessary information [55].
3. The cost of the genetic tests is another challenge as only a few genetic tests are paid for by health insurance companies. The additional financial burden on the patient by bearing the cost of the test constitutes an impediment. However, with proper education, the stakeholders would realize that the benefits of pharmacogenetic testing outweigh the cost of the test [58, 59].
4. Several technical issues are involved in SNP genotyping process before the results can be translated into clinical practice. These include a long duration of time that may be required in the experimental procedure for SNP validation, determination of the most applicable SNPs panels, investigating the correlation that exists between an SNP and enzyme activity, sorting out several low-risk polymorphisms, taking into account that the distribution and frequency of SNPs differ among different ethnic groups and this makes it problematic to apply the findings of one ethnic group to another group.

## CONCLUSION

Inter-individual drug responses due to genetic factors (Pharmacogenomics) constitute a major factor that influences the efficacy and safety of drugs in general. Variability in the genes that encode for the major CYP450 isoforms that mediate the metabolism of antimalarial drugs, contribute significantly to inter-individual drug response. Most healthcare providers are more familiar with the application of non-genetic variables in dosage adjustment strategies but they do not have a clear understanding of the applicability of pharmacogenetic tests to improve therapeutic drug response. However, several resources are freely available to be used in bridging that knowledge gap. Therefore, the introduction of individual SNP genotyping into clinical settings has the potential of providing relevant information regarding dosage adjustment of antimalarial drugs toward achieving optimal drug response.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACT | artemisinin-based combination therapy |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| CQ | chloroquine |
| CYP450 | cytochrome P450 |
| DEAQ | desethylamodiaquine |
| DHA | dihydroartemisinin |
| EM | Extensive Metabolizer |

| | |
|---|---|
| IM | Intermediate Metabolizer |
| PGRN | Pharmacogenomics Research Network |
| PM | Poor Metabolizer |
| SNPs | Single Nucleotide Polymorphisms |
| ULR | unstructured literature review |
| UM | Ultra-rapid Metabolizer |
| WHO | World Health Organization |

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