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Implementing Cytochrome P450 Pharmacogenomics in Clinical Practice: A Glimmer of Hope or Simply a Mirage?

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ABSTRACT

Even though pharmacogenomics approaches are becoming progressively more advanced, opinions on their clinical validity and implementation remain controversial. To ascertain whether cytochrome P450 (CYPs) pharmacogenomics could be favorably implemented in healthcare settings, we reviewed the most recent research as part of this study. The Egyptian Knowledge Bank (EKB) online libraries of Elsevier, Wiley, Springer/Nature, and Sage were searched for a cumulative period that began on January 1, 2015, and ended on December 31, 2023. Priority was given to articles highlighting the application of CYP pharmacogenomics in clinical practice. Six hundred thirteen articles were initially found after an exhaustive search. Based on the inclusion criteria, 26 articles were included. Findings revealed that pharmacogenomics could optimize specific medication prescriptions and reduce potential drug-related problems like the case of tacrolimus. However, more large-scale research could help implement pharmacogenetics testing

in practice settings regarding other medications, such as statins. By implementing pharmacogenomics in healthcare, clinicians can access pharmacogenomic data through web-based technologies. Pharmacogenomics advancement saves time and helps rational medication use depending on the patient's genotype. Our research showed that more pharmacogenomics research is necessary to fully understand the relationship between the presence of genetic variants in CYPs and medication metabolism and response.

Keywords: Pharmacogenomics; Cytochrome P450 (CYPs); Clinical practice; Genetic polymorphism; Pharmacokinetics.

1. Introduction

Pharmacogenomics studies genetic differences in individual medication responses, ranging from potentially fatal adverse drug reactions to a lack of therapeutic effect[1]. This field is rapidly growing and has become more accessible[2]. Pharmacogenomics is a valuable technique for optimizing medication therapy response[3]. This novel approach enables healthcare practitioners to select treatments with optimal efficacy, appropriate dosage, and the lowest risk of significant adverse effects[2] while reducing costs[3]. Many countries worldwide are currently prioritizing the implementation of pharmacogenomics in their clinical settings[4]. This implementation is considered essential to make genomic medicine more widely applicable. This is because genotyping technologies are becoming increasingly available[4].

Pharmacogenetic variations can influence how medications are metabolized and can impact the clinical outcome or efficacy of the treatment[5, 6]. Most drugs bio-transformed by the liver are processed by CYP enzymes, commonly with the CYP1, CYP2, and CYP3 families[6]. The allele distribution of the genes that encode these enzymes varies significantly among populations[6]. For drugs that are metabolized by these enzymes, genetic diversity, particularly in the case of CYP2C9, CYP2C19, CYP2D6, and CYP3A5, is known to have a definite clinical impact[6]. CYP genetic variations significantly impact patients' responses to certain medications, including cardiovascular and narcotic analgesics medications[5, 7, 8]. The medications with the most robust pharmacogenomic evidence are statins, clopidogrel, and warfarin[8]. In addition, the evidence supporting hereditary influences on the response to β-

blockers is increasing[8]. Guidelines are now available for pharmacogenetic test results to optimize the warfarin dose and select the appropriate antiplatelet therapy following percutaneous coronary intervention (PCI). As well, genotyping could estimate the risk of statin-induced myopathy[8]. Furthermore, genotyping results may influence drug selection, therapeutic approaches, or dosage modifications based on the patient's genotype[5].

Pharmacogenomics is becoming more prevalent in the clinical setting and is being integrated into the government-regulated process of medication development[1]. Major agencies like the Food and Drug Administration (FDA) critically review pharmacogenomic data to ensure appropriate incorporation into product labels and successful use of pharmacogenomic techniques in medication development[9]. In this regard, pharmacogenomics information on drug labels is vital for personalizing drugs[10]. Moreover, by leveraging knowledge about the gene-drug pairing for different therapies, healthcare practitioners can make better-informed decisions and provide more personalized care for their patients[2]. Furthermore, to transform this pharmacogenomic data into clinical settings, systems medicine has been implemented by tertiary care institutions to enhance pharmacotherapy[11].

Despite evidence from previous studies pointing to the impact of pharmacogenomics on therapeutic responses, its applicability in ordinary therapy is still up for debate[12, 13]. Pharmacogenomics testing has become more advanced. However, there still needs to be more consensus regarding its clinical rationality and usefulness[14]. Some gaps still exist, like the limited research on the potential benefits of pharmacogenomics testing to improve clinical outcomes[14]. In addition, it is essential to note that there is currently a lack of sufficient data to support the clinical validity and applicability of pharmacogenomics testing for several drugs[13, 14]. However, with concerns about its benefits, pharmacogenomics is gaining popularity[15-19]. Therefore, as part of this study, we examine the most recent research to determine whether CYP pharmacogenomics could be usefully applied in healthcare.

2. Experimental

2.1. Study eligibility

Full-text, peer-reviewed journal publications that are only available in English are included in this review. The chosen articles included review articles, retrospective or prospective

observational studies, and clinical trials. The nominated papers must include implementing CYP pharmacogenomics in clinical practice settings.

2.2. Search strategy

Within the EKB, a vast digital library and an electronic search of the Elsevier, Sage, Springer/Nature, and Wiley databases were limited to the cumulative period from 1/1/2015 to 31/12/2023. Three stages of the investigation were carried out, each based on a different set of queries: ((Cytochrome P450) AND (polymorphism)) AND ((pharmacogenomics) OR (pharmacogenetics)) in phase 1, ((Cytochrome P450) AND (polymorphism)) AND (pharmacokinetics) in phase 2, and ((Cytochrome P450) AND (polymorphism)) AND (personalized medicine) in phase 3. Relevance was assessed in the abstracts of the identified papers. Articles about CYP pharmacogenomics were given precedence. Books, literature written in languages other than English, and content unrelated to the goal were among the exclusion criteria, as shown in Figure 1.

2.3. Selection of articles

To complete the eligibility screening process, we depend on three steps. The titles were assessed for relevancy in the first step. Abstracts were vetted for eligibility at step two. Ultimately, step 3 involved evaluating full-text publications containing chosen abstracts (methodology and outcomes) to determine if they qualified for inclusion in this review. The exclusion criteria included books, duplicate papers, non-English literature, and approaches unrelated to the goals.

2.4. Data extraction

Data were retrieved by (MGM), who evaluated each selected article independently to select the pertinent ones for this review. One researcher (MGM) completed the inclusion process, and in cases where there was doubt about the inclusion of an article, another researcher (MAR) was consulted.

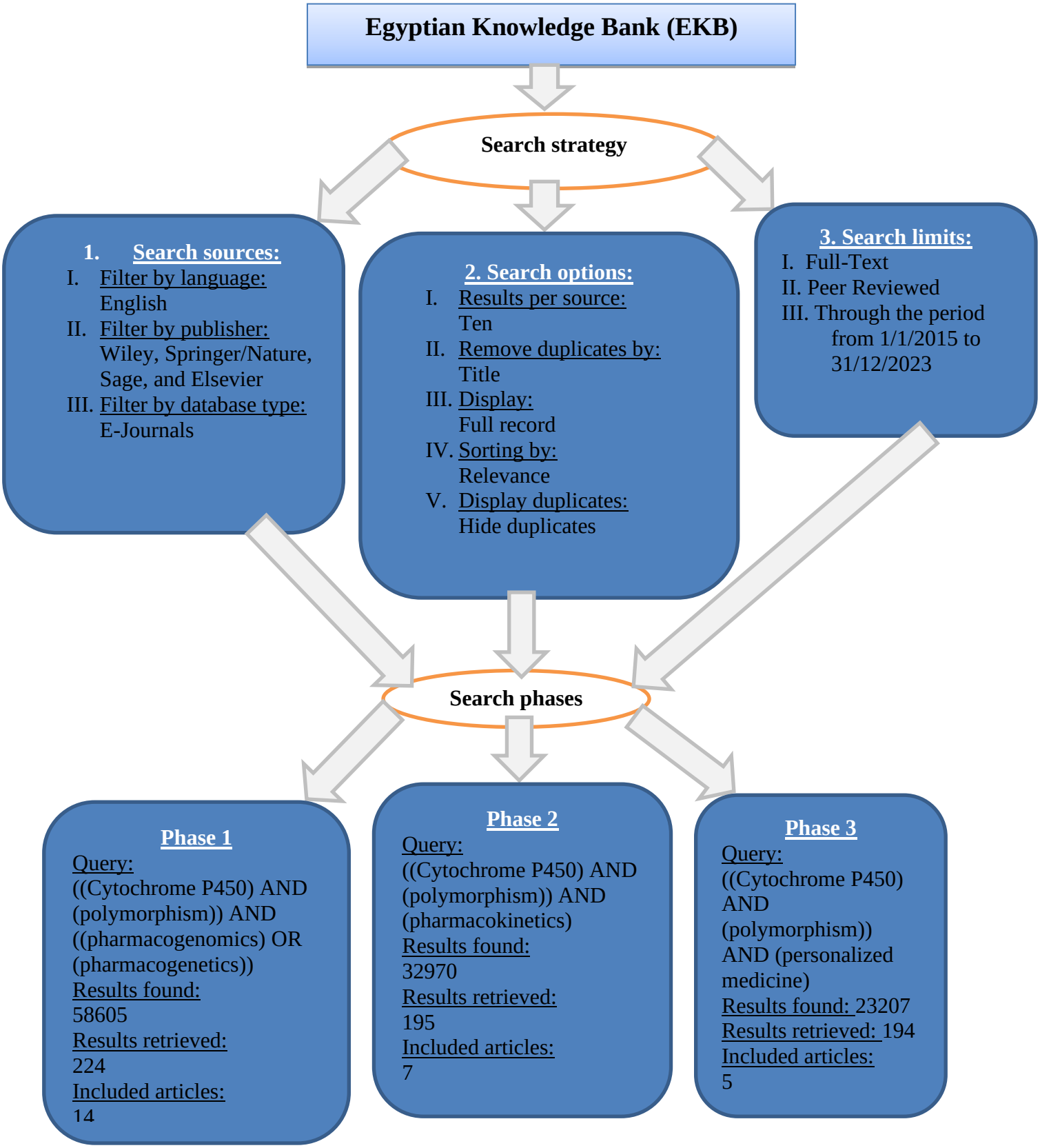

Figure 1. Six hundred thirteen articles were gathered for the preliminary list. After reviewing all abstracts, papers about cytochrome P450 pharmacogenomics were given precedence. Twenty-six papers were included after books and non-English literature were eliminated, and the abstracts were examined for relevancy.

3. Results

3.1. Search Results

Two hundred twenty-four articles from Phase 1, 195 from Phase 2, and 194 items from Phase 3 made up the initial list of retrieved articles (613). Twenty-six articles total (n = 26)—14 from Phase 1, 7 from Phase 2, and 5 from Phase 3—were included after books were excluded and their abstracts were examined for relevancy. This is shown in Figure 1. The 26 articles are shown in Table 1, which also provides an overview of the primary goals of each article that qualified for this review's inclusion.

Table 1. Main objectives of the 26 articles eligible for inclusion in this review.

S.	Author (s)	Main Objective (s)
1	S. A. Brown, et al. 2015[11]	To examine the value of systems-based methods like GWAS[a] in understanding the mechanisms of chemotherapy-induced cardiotoxicity and developing novel cardio-protection strategies.
2	X. J. (Iris) Wang, M. Camilleri. 2019[19]	To review the application of pharmacogenomics to functional GI[b] illness management.
3	A. Urtasun, et al. 2023[20]	To explore the connections between certain different SNPs[c] and optimize the effectiveness of chemotherapy while reducing toxicity and long-term side effects in infants.
4	L. Awdishu, M. S. Joy. 2016[21]	To illustrate the pharmacogenetics of medications and biologics used to treat kidney disorders.
5	W. Y. Shu, et al. 2015[22]	To highlight significant pharmacogenomic findings in the Chinese population and compare the pharmacogenomics of certain widely used medications among the people of China and others.
6	G. D. Velasco, et al. 2016[23]	To determine the possible correlations between adverse reactions and certain SNPs[c] in three core genes involved in the metabolism and transport of sunitinib, everolimus, and temsirolimus.
7	Z. H. Lu, et al. 2018[24]	To review extensively the domains of pharmacogenomics and pharmacogenetics from the perspective of a population-wide approach.
8	L. H. Cavallari, D. L. Mason. 2016[25]	To explain how genetic data, including any information on patients with CKD[d] comorbidity, may guide medication therapy for the treatment of CVDs[e].
9	E. B. Ettienne, et al. 2017[26]	To show how pharmacogenetic testing affects the results of OUD[f] management.
10	N. L. Pereira, et al. 2015[27]	To provide an overview of initiatives integrating pharmacogenomics into clinical practice settings through RCTs[g].
11	G. C. Bell, et al. 2015[28]	To assess the associations between specific SNPs[c] and opioid pharmacokinetics and pharmacodynamics, with a focus on cancer patients.
12	S. D. Denus, et al. 2018[29]	To determine the effects of CYP2C9[h], CYP3A4[h], and CYP3A5[h] gene variations on sildenafil levels assessed in patients with heart failure.
13	N. Ahangari, et al.	To assess the impact of genetic polymorphisms in the vital genes governing the

	2020[30]	metabolism of statins and their significance for personalized treatment in statin-treated patients.
14	X. Zhang, et al. 2018[31]	To demonstrate the feasibility and challenges of utilizing pharmacogenetic information about tacrolimus for applications in clinical settings.
15	J. Y. C. Yang, M. M. Sarwal. 2017[32]	To illustrate how recent genetics and genomics research allowed more advances in understanding graft consequences and organ transplantation diagnostics.
16	T. Kelava, et al. 2020[33]	To review the released research in the past three years that studied the relationships between donor/recipient SNPs[c] and the most prevalent complications following liver transplantation.
17	T. A. M. Mulder, et al. 2021[34]	To demonstrate what is currently known about CYP3A4*22[h].
18	G. N. A. Paulo, et al. 2018[35]	To assess the impact of clinical and gene-related factors on the variation of tacrolimus pharmacokinetics in renal transplantation pediatric recipients.
19	Y.Y. Htun, et al. 2018[36]	To ascertain the frequency of CYP3A5*3[h] allele among kidney transplant recipients from Myanmar and identify the influence of CYP3A5*3[h] polymorphism on tacrolimus level.
20	L. Liu, et al. 2022[37]	To study how polymorphisms in ABCB1[i], CYP3A4/5[h], and POR[j] could impact tacrolimus therapy in juvenile HTx[k] recipients.
21	Y. Choi, et al. 2017[38]	To determine genetic variations that impact tacrolimus pharmacokinetics in healthy male subjects.
22	G. Zhang, et al. 2015[39]	To highlight and rate some pharmacogenomics websites, web links, and significant concepts.
23	J. Reis-Pardal, et al. 2016[40]	To compare the composition, accuracy, and suitability of the pharmacogenetic data presented on US[l] and EU[m] drug labels for using medications in CYP[h] polymorphic metabolizers.
24	R. M. Weinshilboum, L. Wang. 2017[41]	To review the history and evolution of pharmacogenomics and discuss some of the difficulties encountered in applying pharmacogenomics in clinical settings.
25	J. Papastergiou, et al. 2017[42]	To determine how feasible it would be to incorporate personalized medicine services into community pharmacy practices.
26	S. Gupta, V. Jhawat. 2017[43]	To review conventional drug discovery methods and focus on the recent implementation of pharmacogenomics in drug discovery approaches.

a. (GWAS): genome-wide association study, b. (GI): gastrointestinal, c. (SNPs): single nucleotide polymorphisms, d. (CKD): chronic kidney disease, e. (CVDs): cardiovascular diseases, f. (OUD): opioid use disorder, g. (RCTs): randomized clinical trials, h. (CYP): cytochrome P450 enzyme, i. (ABCB1): ATP binding cassette subfamily B member 1, j. (POR): cytochrome P450 oxidoreductase, k. (HTx): heart transplantation, l. (US): United States, m. (EU): European Union.

3.2. Polymorphic CYPs and commonly studied medications

3.2.1. Antitumor agents

Risk of antitumor drugs hematological adverse effects such as thrombocytopenia correlated with SNPs located on CYP genes[20]. In a sample of sixty-four Spanish babies under eighteen months, a study assessed possible correlations between SNPs found in pharmacogenes and responsiveness to antitumor agents. This pharmacogenomic study revealed that

thrombocytopenia risk was significantly increased in the presence of CYP2B6 rs4802101 TC (odds ratio (OR), 1.70; P value < 0.05)[20].

Cyclophosphamide

Cyclophosphamide is a pharmacologically inactive substance biotransformed by CYP 450, particularly CYP2B6, 2C19, 3A4, and 2C9, into 4-hydroxycyclophosphamide[21, 22]. CYP2B6 is considered the major enzyme involved in cyclophosphamide biotransformation[21]. It was demonstrated that in individuals suffering systemic lupus erythematosus nephritis, lacking a minimum of one functional allele of CYP2B6 or 2C19 was linked to a 3.5 times lesser rate of metabolism[21]. In the same context, different genes of CYPs develop interpersonal variation and influence cyclophosphamide adverse reactions[21, 22].

CYPs polymorphisms and cyclophosphamide pharmacokinetics

Pharmacogenetic research illustrated that cyclophosphamide pharmacokinetics is impacted by the genetic variations in the enzymes responsible for biotransformation[21]. The research involved twenty-three male and female patients suffering from Wegener's Granulomatosis and Lupus Glomerulonephritis. Polymorphisms of CYP3A4, CYP2B6 genes were studied[21]. This study showed that CYP2B6 genetic variation was associated significantly with elevated cyclophosphamide plasma levels (P value < 0.05)[21, 22].

CYPs polymorphisms and cyclophosphamide adverse effects

To demonstrate if the CYP2C19 *2 allele was linked to ovarian adverse events in females post Cyclophosphamide therapy, a study included 26 Thai individuals suffering systemic lupus erythematosus[21]. The research found that the carriers of the wild CYP2C19 genotype got the maximum accumulative cyclophosphamide dose. The wild genotype carriers were at higher risk of ovarian adverse effects than the carriers of the genotypes CYP2C19 *1/*2 or *2/*2[21]. Furthermore, another study included sixty-two Caucasian females with systemic lupus erythematosus nephritis adherent to cyclophosphamide[21]. It was designed to show the link between primary ovarian insufficiency and the genetic variation of CYP2C19, 2C9, 3A5, and 2B6. It was found that the carriers of CYP2C19*2 had also a lesser possibility of developing primary ovarian insufficiency[21].

Sunitinib

Molecularly targeted drugs recommended for metastatic kidney cancer (such as sunitinib) are linked to severe toxicities[23]. A study was designated to prove that these severe adverse effects could be expected from genetic variations in particular alleles responsible for the pharmacokinetics of the molecularly targeted agents[23]. In this pharmacogenomics study, 159 Caucasian metastatic kidney cancer patients were recruited and were managed by sunitinib for at least a one-month treatment cycle. All individuals were genotyped for genetic variations in metabolic CYP enzymes CYP3A4 and CYP3A5. Severe toxicity (grade III hypertension) was observed for sunitinib. The study found that the CYP3A4 rs464637 AG allele was linked to a lesser risk of grade III hypertension (P value < 0.05)[23].

Tamoxifen

Genetic variants of CYP2D6 (CYP2D6*10 and CYP2D6*4) are associated with unresponsiveness in about 40% of patients treated with tamoxifen[24]. Lu et al. reported that the CYP2D6*10 genetic variant linked to low enzyme activity is more predominant among Africans and Asians. Furthermore, CYP2D6*4, a nonfunctional gene variant, is more dominant among Caucasians than Asians[24].

3.2.2. Beta-blockers

Carvedilol, and metoprolol undergo metabolism via CYP2D6[25]. In poor metabolizers, elevated plasma levels of these beta-blockers have been observed[25].

3.2.3. Buprenorphine

Ettienne et al. reported that CYP3A4*1B genotyping significantly impacted buprenorphine plasma concentrations and illustrated the influence of drug-gene testing in the treatment of opioid use disorder (OUD)[26]. They analyzed an African American male diagnosed with OUD and was adherent to opioid agonist treatment (buprenorphine/naloxone) over three years. The patient's buprenorphine 24-hour dose was 24 mg, obligated by the prescription benefit manager. However, the patient suffered from physical and behavioral symptoms, and routine urine testing revealed the existence of drugs such as morphine, methadone, and benzodiazepines. The 24-hour dose was increased to 28 mg. Nevertheless, the patient continued to suffer, so drug-gene testing was performed to decide an individualized buprenorphine dose for the patient. The man had the polymorphic allele CYP3A4*1/*1B, inferred as an ultra-rapid metabolic phenotype. This phenotype made the physician raise the 24-

hour buprenorphine dose to 32 mg. Then, illegal drugs were not detected in the patient's urine for more than five months[26].

3.2.4. Clopidogril

Clopidogrel is a prodrug that needs conversion to its active form via CYP2C19[27]. This gene is characterized by its significant genetic variations, including variants that decrease enzyme action, such as CYP2C19*2, *3, *4, *5, *6, *7, and *8[25]. CYP2C19*2 and CYP2C19*3 genetic polymorphisms exist in about 30% of the white ethnicity and 50% of Asians[27]. The decreased plasma concentration of clopidogrel pharmacologically active form may increase the possibility of the development of drug-related severe problems[27]. Several pharmacogenomic research included acute coronary syndrome individuals after PCI[25]. This drug-gene research reported that poor and intermediate metabolizers managed by clopidogrel were at a higher risk of blood coagulation than extensive metabolizers[25].

3.2.5. Cyclosporine A

Kidney transplantation carriers of CYP3A5*3/*3 had high dose-adjusted plasma concentrations[22]. The review of Shu et al. demonstrated that the CYP3A5*3 variant is linked to high dose-adjusted plasma levels in the Han population of the North of China. Besides, the CYP3A4*1G variant is linked to lesser cyclosporine A metabolism than CYP3A4*1/*1 in the Han population of the East of China[22].

3.2.6. Functional gastrointestinal diseases (FGID) treatments

Nortriptyline

Iris Wang and Camilleri. showed that CYP2D6 metabolizes antidepressants used for controlling pain, such as nortriptyline[19]. The study reported that nortriptyline's maximum therapeutic effect can be personalized and obtained based on an individual's pharmacogenomics[19].

Prokinetics

Similar to CYP2C19 polymorphisms, genetic variations of CYP3A4 significantly ($p < 0.05$) affect the metabolism and responses of prokinetics such as cisapride and erythromycin[19].

Proton-pump inhibitors (PPIs)

The majority of common PPIs, except rabeprazole, are deactivated primarily by CYP2C19 so that genetic variations can lead to various patients' responses to PPIs such as lansoprazole, omeprazole, and pantoprazole[19]. Poor metabolizers have high blood levels of

PPIs. The incidence of this genetic polymorphism varies by different ethnic populations. It is more apparent in Asians (15–20% of Japanese) compared with Caucasians (2–6%). On the other hand, ultrarapid metabolizers have decreased PPIs and lowly response to most PPIs[19].

3.2.7. Narcotic analgesics

Variability in patients' response to narcotic analgesics is known and partially relates to polymorphisms of specific CYP genes[28].

Codeine and tramadol

Codeine analgesia relates to its biotransformation into morphine-6-glucuronide and morphine via CYP2D6[28]. Bell et al. illustrated that pain management cannot be achieved in the carriers of CYP2D6 genetic alleles with a decreased enzymatic function. However, individuals with more copies of functional genetic alleles are at high risk of morphine-related toxicities. Tramadol is biotransformed into its more active metabolite (O-desmethyltramadol) via CYP2D6. In this regard, patients with decreased metabolic function genetic variants get less analgesia than others with normal metabolic function genetic variants [28].

Fentanyl

The primary metabolism of the narcotic analgesic fentanyl to its nonfunctional form (norfentanyl) depends on CYP3A5[28]. A study involving 60 cancer Asian individuals whose pain was managed by fentanyl as transdermal patches showed that fentanyl's adverse effects depended on CYP3A5*3 genotypes. In this study, extra and more severe toxicities were observed in the genotype CYP3A5*3/*3 carriers than others with the genotype CYP3A5*1/*1 or CYP3A5*1/*3 ($P < 0.05$)[28].

3.2.8. Sildenafil

The sildenafil dose-adjusted peak concentrations were shown to be linked with the CYP3A4 phenotype in the Caucasian subgroup ($P < 0.05$)[29]. A drug-gene study was designed to assess the influence of CYP450 3A4, 3A5, and 2C9 genetic variations on sildenafil peak plasma concentrations[29]. Sildenafil peak plasma levels were measured at three and six months after the initiation of therapy in 85 patients; 92% of the participants were Caucasians. This pharmacogenetics study was an auxiliary clinical trial study called "Relax". This clinical trial aimed to illustrate the influence of sildenafil in high doses on physical activity and health-related consequences in participants diagnosed with diastolic heart failure (DHF). Participants were genotyped to predict metabolic phenotypes regarding the polymorphic CYP450 3A4, 3A5, and

2C9 alleles. The study found that the CYP3A4 intermediate metabolizer phenotype was linked to higher sildenafil peak concentrations than the extensive metabolizer phenotype after 3 and 6 months of therapy ($P < 0.05$). On the other hand, regarding CYP3A5, poor metabolizer phenotype was associated with apparent high sildenafil peak concentrations. However, the results were not significant ($P > 0.05$). As well, CYP2C9 polymorphisms were not linked to any variations in sildenafil maximum concentrations at the same period of times (P values > 0.05)[29].

3.2.9. Statins

Plasma concentrations of statins like atorvastatin and simvastatin could be substantially impacted when CYP3A4 enzymatic activity is influenced[30]. The affected plasma concentrations could significantly decrease treatment efficacy or increase the risk of adverse effects such as myopathy and rhabdomyolysis[30].

3.2.10. Tacrolimus

The highly genetic variable CYP3A5 enzyme, which has twenty-five genetic variant alleles, plays an important role in about 40 to 50 percent of the variation in response to tacrolimus[31]. The variant alleles CYP3A5*3, *6, and *7 lead to enzymatic dysfunction[31]. The CYP3A5*3, CYP3A5*6, and CYP3A5*7 genetic alleles are linked to differences in tacrolimus trough levels (TTLs)[21, 25, 31-33]. Likely, the allele CYP3A4*22 has a great negative impact on the enzymatic activity of CYP3A4[34]. The CYP3A4*22 variant greatly affects tacrolimus pharmacokinetics[34]. This allele reduces tacrolimus metabolism, enhancing the possibility of reaching supratherapeutic drug levels[31].

Spanish subjects

A study found that CYP3A5 genotyping elucidates variations of about 60% of TTLs ($P < 0.05$) and 21% of peak levels ($P < 0.05$)[35]. This study included 21 pediatric Spanish participants who had renal transplantation and were managed by tacrolimus one month before the study initiation. After genotyping for CYP3A5, all individuals were either "CYP3A5 expressers or non-expressers". Expressers individuals were carriers of one or two CYP3A5*1 alleles (*1/*1 or *1/*3), and CYP3A5 non-expressers were not (*3/*3). From the total twenty-one participants, 17 subjects were non-expressers whose tacrolimus trough, peak concentrations, and 24-hour AUC were 210, 72, and 119% greater than expressers[35].

Myanmars subjects

CYP3A5 genetic variations affected tacrolimus pharmacokinetics; Initial concentration/dose ratio (C0/D) in research recruited 41 Myanmars renal transplantation recipient patients[36]. Of the total kidney transplantation recipients (n = 41), 25 (60.97%) and 16 (39.02%) had CYP3A5 nonexpressors and expression, respectively[36]. The tacrolimus C0/D in the expressors was lower than in the nonexpressors after one and three months of therapy ($P < 0.05$ and < 0.0001, correspondingly)[25, 31, 36].

Chinese subjects

In juvenile heart transplantation (HTx) recipients, a study examined the impact of CYP3A4/5 on tacrolimus pharmacokinetics in the initial post-surgery phase[37]. Sixty-six pediatric Chinese HTx receivers were recruited and divided into three groups depending on their age (< 6, from 6 to 12, and > 12- to 18-year-old). In the pediatric receivers six years old or more, there was a strong correlation between CYP3A5*3/CYP3A4*1G and tacrolimus C0/D and dose requirement ($P < 0.05$)[37]. In the same context, the review of Shu et al. found that concerning the Chinese population, the CYP3A5*3 variant was linked to significantly high tacrolimus plasma drug levels[22]. In addition, the carriers of the CYP3A4*1B variant demonstrated significantly lesser Co/D than others that carried the homozygous wild allele[22]. However, Shu et al. reported that CYP3A4*1B genetic variation could not be the topmost reason for the tremendous interpersonal variation of this immunosuppressant pharmacokinetics[22]. Furthermore, concerning the CYP3A4*1G variant that frequently presents in Asians, plasma trough concentrations in carriers of CYP3A4 *1/*1 were significantly high ($P<0.05$) among the Han population of the South of China[22]. The review found that the tacrolimus levels were significantly higher in CYP3A4 *1/*1 carriers than in the carriers of *1/*1G and *1G/*1G[22].

Korean subjects

A drug-gene study reported that genetic polymorphism of CYP3A5*3 and NR1I2, a known controller of CYP3A4 expression, impacted tacrolimus pharmacokinetics[38]. These genetic polymorphisms were responsible for the unpredictability in 54% of tacrolimus area under the curve from time zero to time of last assessable concentration (AUClast). For this drug-gene study, "the Drug Metabolizing Enzymes and Transporters (DMETTM) Plus platform (Affymetrix et al.)" was used, and 1888 genetic biomarkers were tested. However, 1223 total biomarkers were not polymorphic in the study participants, so this drug-gene study included only

665 biomarkers in the ultimate genomic information analysis. Both tacrolimus peak level (Cp) and AUClast were determined in 42 healthy male Korean participants[38]. The means of Cp and AUClast were higher in the case of the genotype (CYP3A5*3/*3) than the genotype (CYP3A5*1/*1)[25, 31, 38]. The Cp and AUClast percentage increase were 164% and 278%, correspondingly (P<0.05)[38].

African American subjects

A Genome-wide association study (GWAS) determined TTLs in recipients of African American kidney allografts[32]. This genetic study showed that CYP3A5*6 (rs10264272), CYP3A5*7 (rs41303343), and CYP3A5*3 (rs776746) variants were independently and significantly linked to TTLs ($P < 0.05$). The observed variance in troughs is explained by all three alleles plus clinical factors in 53.9% of the total 357 studied cases. While, clinical and demographic factors contributed 19.8% of the variance[32].

3.2.11. Warfarin

Drug-gene screening provides optimum warfarin dose and allows the recommendation of rational antiplatelet treatment following PCI[25]. The CYP2C9 gene plays a vital role in warfarin metabolism[22]. Modern research links between genetic variants of CYP2C9 and warfarin bleeding risk[25]. CYP2C9 polymorphisms are linked to diminished S-warfarin metabolism and lesser anticoagulant dosage requirements. CYP2C9 genetic variants *2 and *3 are viral concerning warfarin dosing requirements[25]. In the Caucasian population, both CYP2C9*2 and CYP2C9*3 alleles decrease warfarin activity by about 30% and 80%, respectively[22]. Therefore, the carriers of these genetic variants should receive lesser warfarin doses, particularly CYP2C9*3/*3 carriers. Nearly all Han populations do not carry CYP2C9*2[22]. Furthermore, genetic variants such as CYP2C9*5, *6, *8, and *11 decrease warfarin metabolism and are widespread in Africans [22, 25]. Likely, CYP4F2 genetic polymorphism is linked to warfarin dose variation that was proven by thirty researchers, including nine thousand subjects[22]. In addition, the review by Shu et al. showed that the polymorphism of CYP2C18 was significantly ($P < 0.05$) related to warfarin dosage among the Han population of Taiwan and China[22].

3.3. Pharmacogenomics and practice settings

3.3.1. Pharmacogenomic data resources

Population-wide polymorphisms show that drug therapies are only useful to a group of patients, with the other patients either untreated or having adverse drug reactions[24]. Around 19,000 genetic polymorphisms from about 1600 humanoid genes have been included in various easily accessible genetic databases[24]. Zhang et al. in his review reported that, at present, copious pharmacogenomic data resources are available due to the advances in pharmacogenomics, including whole genome association studies and sequencing technologies[39]. This review presents specific pharmacogenomic web resources and gives a star rating to each resource. Accordingly, the best five-star web resources included PharmGKB, DrugBank, and the FDA's pharmacogenetic website. The PharmGKB web resource provides esteemed pharmacogenomic data such as genotype-based summaries and associations between drugs and genetic variants. DrugBank web resource delivers valuable pharmacogenomic data such as drug pharmacogenomics and metabolic enzymes. FDA's pharmacogenetic website provides appreciated pharmacogenomic data such as variability in drug exposure and clinical response and dosing recommendations depending on genotypes[39].

3.3.2. Drug labeling

CYP genetic information in drug labeling is of great importance as this allows the rational use of medications in case of different metabolic phenotypes[40]. The study by Reis-Pardal et al. demonstrated that the officially approved drug labels by the United States (US) FDA and European Union (EU) included pharmacogenetic information[40]. The EU labels are called EU Summaries of Product Characteristics (SmPCs). This study compared what was included about CYP450 pharmacogenetics in the US FDA-approved drug labels with the equivalent EU-approved SmPCs. His research found that almost 75% of the evaluated US labels had superior overall quality scores(P values < 0.05). The study also demonstrated that the US labels were significantly widespread, better in structure, and provided more information ($P < 0.05$)[40].

Clopidogril label

The FDA modified the official clopidogrel label to support healthcare practitioners' decisions concerning clopidogrel prescription [27]. The modified label includes an antiplatelet medication different from clopidogrel, which should be used in the carriers of the genetic variants associated with reduced clopidogrel metabolism[27].

Certain medications labels

The FDA modified the official labels of carvedilol, metoprolol, propranolol, statins, propafenone, warfarin, isosorbide, and hydralazine to include pharmacogenetic data to help physicians regarding the recommendation of these medications[27]. For instance, the labels of carvedilol, metoprolol, propranolol, and propafenone illustrate the influence of the different CYP2D6 metabolic phenotypes on medication pharmacokinetics. Furthermore, the official medication label of warfarin currently includes doses depending on polymorphisms of CYP2C9[27].

3.3.3. Pharmacogenomics and time saving

The time-consuming classical genotyping currently could be replaced by time-saving "point of care" genotyping platforms such as "The Spartan RX™ CYP2C19 genotyping platform (Spartan Biosciences, Canada)" [27]. This approach depends on buccal swabs to demonstrate the genetic variant CYP2C19*2 or *3 carriers within one hour. In only two hours, such pharmacogenomic screening helped warfarin drug-gene clinical studies offer warfarin dose-related information based on individual genotypes[27].

3.3.4. Systems medicine

As an emerging approach, great academic hospitals have applied systems medicine to translate pharmacogenomic data into clinical practice and prevent drug adverse events[11]. Systems medicine can be achieved by applying systems-based approaches like GWAS, candidate gene studies, genomic profiling, proteomics, and mathematical and computational modeling in answering clinical questions. Cardio-oncology can benefit from systems medicine that involves screening, monitoring, and managing patients with adverse cardiovascular events from anticancer agents. Furthermore, pharmacogenomics improvements show many biological pathways and genetic polymorphisms associated with cardiotoxicities from medications such as doxorubicin and trastuzumab[11].

Pharmacogenomic data in electronic health records (EHRs)

Weinshilboum and Wang’s review showed that pharmacogenomics influences almost all medicinal domains[41]. The study demonstrated the US-FDA pharmacogenomics website list of 127 medications with their clinically significant genetic biomarkers. This review showed that patients' genomic data could be stored in EHRs that efficiently provide genomic information to healthcare practitioners, where, particular drug-gene tests could be recommended. Great health

centers like Mayo Clinic depend on automated computerized systems. These advanced systems warn health care practitioners when one of the pre-specified listed seventeen medications that require a drug-gene test is recommended. In this context, the Mayo Clinic developed research called "RIGHT study -RIGHT drug at the RIGHT dose at the RIGHT time" to confirm the value of this imperative issue. This research involved sequencing the DNA of 1013 patients. At that point, the patients' electronic medical records included the pharmacogenomic sequencing results. Warnings were given to healthcare practitioners after prescribing one of the Mayo Clinic's pre-specified medications list. However, warnings were not given to recommend specific drug-gene tests but with the patient's pharmacogenomic information associated with the clinical significance[41].

3.3.5. Drug-gene testing in community pharmacies

A study by Papastergiou et al. assessed community pharmacies' ability to provide individualized medicine[42]. The study evaluated if the pharmacies could determine the number of adverse medication events after offering drug-gene testing[27, 42]. This research was performed in two activity community pharmacies in Toronto, Ontario[42]. Pill check was used as a genotyping technique. It can determine genetic polymorphisms associated with changes in the pharmacokinetics of more than one hundred commonly clinically used drugs. In this Canadian research, pharmacists detected medication-related problems and then asked the 100 participants to go to a health center to judge the data they obtained. Of the total patients, 10.4% required a new medication, 32.6% had medications adverse events, and 43.0% suffered ineffectiveness. The mean of medication treatment problems linked to drug-gene screening was also found to be 1.3/patient. Community Pharmacists recommended either modification in treatment(60.3%), correction of dose(13.2%), stoppage of treatment (4.4%), or follow-up more than before(22.1%). The study also illustrated that some drugs necessitate drug-gene testing, such as antidepressants (33.9%), statins (22.1%), PPIs (12.6%), and clopidogrel (12.6%)[42].

3.3.6. Pharmacogenomics and medication development

Gupta and Jhawat showed that using pharmacogenomic data in medication development improves the assessment of medication distributions, actions on binding sites, and metabolism[43]. The traditional methods used to discover medications cost too much, take a long time, and are extremely difficult. However, this development's dependence on functional and structural pharmacogenomics enhances medication innovations. They illustrated that the

functional drug-gene approach involves gene expressions and linkage analysis. On the other hand, the structural drug-gene approach involves mapping, DNA sequencing, and SNPs[43].

4. Discussion

Pharmacogenomics has been gaining popularity in medicine; however, some doubts exist about its benefits[15-19]. Accordingly, through this investigation, we review the recently published literature to assess if implementing CYPs pharmacogenomics in clinical practice settings could add value.

4.1. Polymorphic CYPs and commonly used medications

4.1.1. Antitumor agents

Polymorphisms of both CYPs impact the response to antitumor agents such as cyclophosphamide, sunitinib, and tamoxifen[21-24].

Cyclophosphamide

CYP2B6 genetic variation was linked to significantly high cyclophosphamide plasma levels[21, 22]. However, other research showed conflicting results regarding the relation between CYP2B6 and cyclophosphamide pharmacokinetics and treatment goals[22].

Given that, pharmacogenetic aspects that can anticipate cyclophosphamide treatment responses in renal disorders and renal-related toxicities are progressing. Further studies would assist the application of such results in practice settings[21].

Sunitinib

CYP3A4 is the key enzyme responsible for sunitinib metabolism, the active metabolite SU12662, and its deactivation[44]. This review explains Genovefa Kolovou et al.'s finding illustrating the association between CYP3A4 rs464637 AG allele and sunitinib adverse reactions in metastatic kidney cancer patients[23].

Additional research is required to justify this result and prove that sunitinib's adverse effects could be predicted by the CYP3A4 genetic variation[23].

Tamoxifen

CYP2D6*10 and CYP2D6*4 alleles are allied to unresponsiveness to tamoxifen therapy[24]. Specific research found contradictory results[45]. However, the FDA has approved pharmacogenetic tests for CYP2D6-polymorphisms before tamoxifen treatment[24].

Accordingly, the common CYP2D6*10 allele in Africans and Asians, besides the predominant CYP2D6*4 variant in Caucasians, should be identified before tamoxifen treatment[24].

4.1.2. Beta-blockers

Carvedilol and metoprolol plasma levels were elevated in poor metabolizer phenotype[25]. However, Does et al. showed that both beta-blockers were safe even at high plasma concentrations[46].

Therefore, in the case of decreased metabolic enzyme activity, the elevation of beta-blockers plasma levels is not of clinical significance due to their safety over wide plasma therapeutic level ranges[25].

4.1.3. Buprenorphine

Picard et al.'s in vitro study, showed that CYP3A4 is the primary CYP metabolic enzyme responsible for buprenorphine metabolism[47]. This finding was consistent with the E. B. Ettienne et al. report that CYP3A4 polymorphism made the physician change the buprenorphine daily dose[26].

Therefore, high buprenorphine 24-hour dose is required in ultra-rapid metabolizers.

4.1.4. Clopidogril

CYP2C19 enzyme converts clopidogrel (prodrug) to the active form[27]. This is consistent with Cavallari and Mason's report that the official clopidogrel labeling (FDA) includes a notice about reducing medication response in poor metabolizers[25]. Likely, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends another antiplatelet medication for both poor and intermediate metabolizers after acute coronary syndrome or PCI. Furthermore, the American College of Cardiology and the American Heart Association recommend CYP2C19 screening after acute coronary syndrome or PCI if the patient's genotype could influence antiplatelet therapy. In the same context, in June 2012, CYP2C19 screening following PCI was initiated at the University of Florida Health (UF Health). Moreover, patients' electronic medical records and computer-based prescribing at UF Health support healthcare providers' decisions by providing warnings in case of prescribing clopidogrel for poor or intermediate metabolizers. In this regard, the electronic prescribing system at UF Health recommends ticagrelor or prasugrel if possible[25].

Given that, genotyping may enhance clopidogrel prescribing and reduce adverse events.

4.1.5. Cyclosporine A

In several studies, renal transplantation Chinese patients carrying the CYP3A5*3/*3 genotype had high dose-adjusted cyclosporine A plasma concentrations [22]. However, other research illustrated inconsistent results[22]. In this context, the French Anglicheau et al. study concluded that CYP3A5 polymorphism did not significantly impact the pharmacokinetics of cyclosporine[48]. This discrepancy can be explained by the fact that the Chinese drug-gene studies are done in discrete research centers, so the findings may need to be more consistent or challenging to popularize [22].

Thus, in this regard, clinical trials involving many medical institutions, subjects, and long periods are required for more precise findings that can be generalized.

4.1.6. FGID treatments

Wang and Camilleri's review showed that polymorphisms of CYP2D6, 2C19, and 3A4 had a seeming effect on FGID treatments such as; nortriptyline, prokinetics, and PPIs[19]. In this regard, Agyeman and Asenso's research illustrated that more investments are required to initiate more pharmacogenetic research and develop more pharmacogenomic biomarkers[49].

Consequently, the occurrence of polymorphisms associated with these medication's metabolism and response necessitates extra pharmacogenomic studies.

4.1.7. Narcotic analgesics

According to Gaedigk's review, CYP2D6 metabolizes 25% of clinically used medications, including several opioids, antidepressants, and antipsychotics[50]. This report agreed with Bell et al. study that CYP2D6 polymorphisms had an apparent influence on narcotics response and adverse effects[28]. This study reported that treatment failure, including toxicities, inability to manage pain, or both, was linked to carriers of specific CYP2D6 genetic variants who received narcotics (codeine or tramadol)[28]. Regarding fentanyl, in Bell et al.’s study, CYP3A5 played a crucial role in its metabolism[28]. However, Dong et al.’s research demonstrated that the CYP3A4*1G allele impacted fentanyl effectiveness[51].

As a result, drug-gene screening and clinical trials associated with polymorphisms of genes responsible for narcotics pharmacodynamics and pharmacokinetics are necessary to tailor narcotic analgesic therapy.

4.1.8. Sildenafil

The research of Denus et al. found that the CYP3A4 phenotypes were associated with sildenafil peak plasma concentration levels in Caucasians[29]. Nevertheless, Ku et al.'s investigation illustrated that genetic variation in another gene, CYP3A5, influenced the pharmacokinetics of specific phosphodiesterase type 5 inhibitors such as sildenafil[52].

Given that, the application of this outcome in clinical practice needs additional clinical research.

4.1.9. Statins

The metabolic enzyme CYP3A4 significantly affects atorvastatin and simvastatin plasma concentration levels[30]. CYP3A4 genetic polymorphisms were associated with variations in response to statin therapy[30]. However, the investigation of Gao et al. concluded that the CYP3A4*1G allele affected atorvastatin efficacy significantly and had no noteworthy influence on response to simvastatin[53]. Moreover, a study conducted on the Indian population did not demonstrate a significant correlation between low levels of LDL-C following atorvastatin medication and the CYP3A4*1B genetic variant[30, 54, 55].

Consequently, the most well-known gene, CYP3A4, impacts the metabolism of certain statins. However, further pharmacogenomic research is required concerning SNPs that can predict response to statins.

4.1.10. Tacrolimus

CYP3A4 and CYP3A5 genetic polymorphisms are associated with variations in tacrolimus trough concentrations that should be kept at definite levels to avoid adverse drug events[32, 35]. However, Choi et al. reported that there is contradictory available research about associations between pharmacogenomics and tacrolimus pharmacokinetics, except the influence of CYP3A5*3 polymorphism on this immunosuppressant pharmacokinetics[38]. A clinical study revealed that adjusting tacrolimus doses depending on CYP3A5 genotyping reduced the required duration to attain optimum medication levels more than the ordinary dose method [25]. Besides, CPIC recommends that the initial elevated tacrolimus dose in CYP3A5 gene expression be 1.5-2 folds more than the frequently used dose[25]. Furthermore, Awdishu and Joy demonstrated that CYP3A5 genotyping could help particularly in tacrolimus dosing procedure and attaining aimed plasma levels more rapidly[21]. In this context, the research of Zhang et al. concluded that transforming pharmacogenetic data into practice settings may provide rational use of

tacrolimus[31]. However, genotype screening was seldom implemented due to monetary or practical causes[31].

Accordingly, genotyping for CYP3A5*3 and implementing this data into healthcare settings could help avoid adverse events such as acute transplant rejection.

4.1.11. Warfarin

Tan et al.'s review concluded that CYP2C9 genotyping provided the chance to fulfill the dreams of personalized medicine[56]. Furthermore, the warfarin regimen could be tailored and prescribed according to genetic data[56]. In this regard, Cavallari and Mason's study reported that many organizations implemented drug-gene screening as an essential clinical aspect to advance the individualization of warfarin treatment[25]. In the University of Illinois Hospital & Health Sciences System (UI Health), warfarin dose recommendation relies on genotyping for hospital-admitted individuals. The genotyping approach developed more effective anticoagulation and fewer adverse events. In this context, the official warfarin labeling (FDA) was modified in 2007 to include a lesser initial dose for carriers of CYP2C9*2 or CYP2C9*3[25].

Thus, genotyping may enhance warfarin medication prescribing by choosing the proper doses for the right patient.

4.2. Pharmacogenomics and practice settings

4.2.1. Pharmacogenomic data resources

Abundant pharmacogenomic resources make data regarding genetic polymorphisms available and easily accessible[39]. In this respect, the study of Glubb et al. concluded that the Internet is a beneficial tool for pharmacogenomics[57]. Many websites offer access to data from clinical and genetic studies besides tools that could be used to analyze results or develop theories[57].

Consequently, using web-based tools, researchers, physicians, and patients could quickly obtain pharmacogenomic data concerning necessary DNA sequences, genotypes, phenotypes, and bioinformatic data.

4.2.2. Drug labeling

Medication labels that include CYP genetic information enable the appropriate administration of drugs for patients with various metabolic phenotypes[40]. In that regard, the

research of Reis-Pardal et al. showed that the FDA-approved drug labels provided more specific pharmacokinetic information for CYP polymorphic metabolizers than the EU-approved SmPCs[40]. Conversely, as the EU SmPC is updated continuously by European Medicines Agency (EMA) regulations[58], quality discrepancies with US labeling should steadily narrow[40].

From this perspective, these regulatory organizations should coordinate with each other and concurrently insert pharmacogenetic information into drug labeling to achieve worldwide synchronization and get rational medication use.

4.2.3. Pharmacogenomics and time saving

Rusnak et al.'s review reported that pharmacogenomics may result in better adherence, a shorter time to the best possible disease management, and less morbidity and mortality [59]. This report is consistent with Pereira et al.'s study that illustrated the availability of obtaining the warfarin dose-related information depending on genotyping within only two hours[27].

Therefore, through improvements in technologies and programming, pharmacogenomics evolution saves time and provides the proper medication with the correct dose to the right patient.

4.2.4. Systems medicine

The patient's EHRs could contain pharmacogenomics data[41]. At that point, alarms could be provided to medical professionals following the prescription of certain pre-specified medications[41]. In this context, the review of Wilke et al. found that genotyping and healthcare information technology are developing quickly, opening up new avenues for scientific and medical research[60]. Furthermore, the investigation of J. F. Peterson et al. concluded that for new genomic services to be introduced successfully, EHRs should translate pharmacogenomic data into clinical practice[61].

Clinical notifications of high-priority pharmacogenomics results, such as those linked to severe adverse events, could be integrated into EHRs for the transformation of genomic data into clinical care.

4.2.5. Drug-gene testing in community pharmacies

Papastergiou et al. found that community pharmacies could evaluate adverse medication events following offering pharmacogenomic testing[42]. Rendell et al. research agreed with this

finding; drug-gene tests in community pharmacies involve patients' cheek swab samples of their DNA[62]. Following the receipt of data from a laboratory, community pharmacists can evaluate the patient's prescription regimen and suggest changes to the prescribers[62].

Drug gene testing as a genomic service could be delivered quickly through community pharmacies.

4.2.6. Pharmacogenomics and medication development

Gupta and Jhawat demonstrated, utilizing pharmacogenomic data in drug development, enhances the evaluation of drug distributions, activities on binding sites, and metabolism[43]. Surendiran et al. agreed with this result[63]. The research concluded that drug discovery and therapy success could be influenced by pharmacogenomics, a significant new theme in the medical sciences. With the development of pharmacogenetic research, the two principal aspects that determine a novel drug's success, safety and efficacy, could be more predictable[63].

Therefore, advances in pharmacogenomics could enhance the development of drugs through the simple anticipation of different patients' responses to the novel medications according to their genotypes.

5. Conclusion

Though its benefits are debatable, pharmacogenomics has become increasingly popular in the medical community[15-19]. Therefore, as part of this study, we examine the most recent research to determine whether CYP pharmacogenomics could be usefully applied in clinical practice settings. Our study revealed that the presence of CYP genetic variations linked to medication metabolism and response requires further investigation in pharmacogenomics. Further large-scale studies will help apply such results in practice settings regarding certain medications (cyclophosphamide, sunitinib, cyclosporine, FGID treatments, narcotics, sildenafil, and statins). This research also demonstrated that the predominant CYP2D6*10 allele in Africans and Asians, besides the common CYP2D6*4 variant in Caucasians, should be identified before tamoxifen therapy. In addition, a high buprenorphine daily dose is necessary in the case of ultra-rapid metabolizers. Further, genotyping could enhance clopidogrel, tacrolimus, and warfarin prescriptions and decrease the potential adverse events. Regarding beta-blockers, this research demonstrated that in poor metabolizers, plasma level elevations were not clinically significant due to their safety over broad plasma level ranges. With the implementation of

pharmacogenomics in clinical practice, healthcare practitioners could easily access pharmacogenomic data using web-based tools. Pharmacogenomics evolution, through improvements in technologies, systems, and EHRs, saves time and provides the proper medication with the correct dose to the right patient. Furthermore, this investigation showed that genomic service could be delivered quickly through community pharmacies. Moreover, recent progress in pharmacogenomics could enhance the development of novel drug compounds by predicting their safety and efficacy according to patients' genotypes. Our findings revealed that implementing CYP pharmacogenomics in clinical practice has yet to be ultimately achieved. However, translating the readily available genomic data into clinical settings would add significant value to routine medical care. Pharmacogenomics would enhance therapy's effectiveness, reducing both the cost of therapy and adverse events.

Recommendations and Future Directions

There's a chance that predicting patients' safe and successful response may be achieved by tailoring medication based on their genotypes. Ongoing education programs about drug-gene pairings would further empower healthcare professionals to customize pharmaceuticals depending on individuals' genetic makeup. Improving clinical outcomes for patients is considered a top priority for tertiary care facilities. One way to achieve this is by incorporating computer modeling technologies to support and enhance pharmacogenomics. This approach has the potential to personalize treatment plans and medication choices, ultimately leading to better patient care and improved health outcomes. This integration would enable the identification of interpersonal differences in sensitivity to specific toxicities or adverse reactions, allowing healthcare professionals to recommend rational medications.

- **Conflict of Interest**

The authors declare that they have no conflict of interest with this work.

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