A Study on Pharmacogenomics in Clinical Practice

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ABSTRACT: ***Pharmacogenomics is a rapidly developing discipline that has important therapeutic implications for customizing medications to enhance effectiveness and/or decrease toxicity. Several definitions of provision is made have already been proposed by professional organizations, regulatory agencies, or researchers. The goal of this review is to examine the practical use of pharmacogenomics for certain pharmacological treatments (e.g., protons pump inhibitors, codeine, or carbamazepine), as well as the limits and obstacles that prevent pharmacogenomics from being implemented in clinical practice. Drug disposition and/or reaction are influenced by genetic polymorphisms in cytochrome P450 (CYP) enzymes as well as the existence of the human leukocyte antigen (HLA)-B*1502 allele. The CYP2C19 genotype can explain a fraction of PPI pharmacokinetic or pharmacodynamic variability. However, research on Helicobacter pylori cure rates depending on the CYP2C19 genotype is mixed. Adverse drug responses in neonates from CYP2D6 ultra-rapid metabolizers have been observed in codeine through breast-feeding. However, there isn't enough information to say if CYP2D6 polymorphisms affect codeine effectiveness and toxicity in general. Despite the availability of CYP2C19 or even CYP2D6 genotyping assays, their clinical usefulness is limited. Carbamazepine-induced Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis are linked to the HLA-B*1502 allele (TEN). Prior to starting carbamazepine in high-risk individuals, pharmacogenomic testing is necessary. Several constraints and obstacles to adopting pharmacogenomic testing in clinical practice include a lack of resources, provider competence, and ethical, legal, as well as societal concerns.***

KEYWORDS: ***Codeine, Clinical, Pharmacogenomics, Pharmacogenetics, Carbamazepine.***

1. INTRODUCTION

Pharmacogenomics is a fast-evolving science with significant therapeutic implications for personalizing medication to improve efficacy and/or reduce toxicity. Professional organizations, regulatory bodies, and researchers have suggested several, but similar definitions of pharmacogenetics/pharmacogenomics. The study of genetic origins of individual differences in medication response is referred to as pharmacogenetics. 1 Pharmacogenomics is defined as the study of genetic factors of medication effectiveness and toxicity across the genome. 2 Pharmacogenomics analyses genes across all chromosomes, whereas pharmacogenetics concentrates on a single usually a few genes. Although the terms pharmacogenetics as well as pharmacogenomics are interchangeable, for the purposes of this review, pharmacogenomics shall be utilised. This article addresses the pharmacogenomics of certain pharmacological treatments, as well as the limitations and problems of using pharmacogenomics testing in clinical settings[1].

1.1.Identifying Polymorphisms and Their Clinical Implications:

In terms of functional effect, population prevalence, and clinical importance, a polymorphism for a given protein might differ. As a result, it is proposed that polymorphisms be studied in a methodical manner. Because polymorphisms typically impact proteins, it is critical to first identify the polymorphism. Enzymes, drug transporters or receptors are examples of genetically polymorphic proteins, with functional effects ranging from enhanced to reduce to no change in protein activity. The next stage is to determine if a polymorphism has population variation. There are cases where a polymorphism is seen at a greater frequency in a particular ethnic group. Relationships between the polymorphism and drug and illness for a person should be investigated when evaluating clinical significance. The polymorphism may impact drug dosage, effectiveness, toxicity, pharmacokinetics, and/or pharmacodynamics. A polymorphism can also affect illness prognosis, susceptibility, or be utilised as a disease screening test.

1.2.Examples of Pharmacogenomics in Clinical Practice:

History. PPIs (omeprazole, pantoprazole, esomeprazole, lansoprazole, dexlansoprazole, as well as rabeprazole) are used to treat a variety of acid-related diseases in the stomach (eg, gastric ulcer, gastroesophageal reflux disease, Zollinger-Ellison syndrome, and duodenal ulcer). For Helicobacter pylori (H pylori) eradication, they're used with one or two antibiotics. PPIs are irreversible inhibitors of the H/K

ATPase pump, which has an effect on acid output in the stomach. PPI pharmacokinetics have been extensively reviewed elsewhere. CYP2C19 and, to a lesser extent, CYP3A metabolize omeprazole, esomeprazole, lansoprazole, and pantoprazole. The degree of CYP2C19 and CYP3A metabolism varies amongst PPIs, however. Rabeprazole is mostly metabolized to a thioether by nonenzymatic reduction[2].

As in Context of FDA-Approved Drug Labels, a List of Selected Clinically Valid Pharmacogenetic Biomarkers as well as Levels of Recommendation For Related Drugs, show in table 1.

Table 1: In the context of FDA-approved drug labels, list of clinically valid pharmacogenetic biomarkers but also level of recommendation for related drugs

Pharmacogenetic Marker	Representative Drug	Disease	Test Name
c-KIT expression +	Imatinib	Gastrointestinal stromal tumor	Dako Cytomation c-Kit pharmDx
CCR5 expression +++	Maraviroc	HIV infection	Trofile
CYP2C9 variants; VKORC1 variants ++	Warfarin	Thromboembolism	Verigene Warfarin Metabolism Nucleic Acid Test
CYP2D6 variants +	Atomoxetine, fluoxetine	Attention-deficit hyperactivity disorder, depression, obsessive-compulsive disorders	Roche Ampli Chip CYP450 test
DPD deficiency +	Capecitabine, 5-FU	Colorectal cancer	Thera Guide 5-FU
EGFR expression +	Erlotinib	Non–small-cell lung cancer	Dako Cytomation EGFr pharmDx
G6PDH deficiency +	Primaquine	Malaria	Glucose-6-phosphate dehydrogenase screening

1.3.Clinical Relevance:

There are presently no published studies that have evaluated PPI dosing methods depending on CYP2C19 genotype, despite the fact that H pylori dual/triple treatments for eradication differ in terms of PPI usage and dose. This might be owing to PPIs' wide therapeutic window, low frequency of clinically relevant side effects, and wide range of dual/triple treatment regimens. Higher PPI dosages have been suggested for homozygous EMs, although this has yet to be adopted in clinical practice. The bulk of therapeutically relevant research has been on the influence of CYP2C19 genotypes on H pylori eradication, with little consideration paid to the possibility of adverse effects. The pharmacokinetic (PK) and pharmacodynamic (PD) variability of PPIs is unique. PMs had a 7- to 14-fold greater omeprazole area under the concentration–time curve (AUC) than homozygous EMs. Omeprazole AUC is related to intragastric pH with PMs having greater intragastric pH values than EMs. Antibiotic concentrations and bioavailability and stability have been demonstrated to increase with a higher intragastric pH. PPI PK and PD variations, which are partially explained by CYP2C19 genetic variants, have resulted in varying H pylori cure rates. In one research, Japanese patients with proven H pylori infection were given omeprazole and amoxicillin for many weeks as a combination treatment. In homozygous EMs, heterozygous EMs, and PMs, respectively, cure rates for H pylori were 28.6%, 60%, and 100%. These findings are in line with the bulk of omeprazole research. Furthermore, numerous meta-analyses have indicated that the effectiveness of omeprazole is dependent on the CYP2C19 genotype[3], [4].

1.4.Availability and Recommendations Testing:

For CYP2C19 genotyping, a commercially accessible FDA-approved test (AmpliChip1 CYP450, Roche Diagnostics, Indianapolis, IN) is available. A complete blood sample is taken, DNA extracted, as well as the presence or absence of CYP2C19*2 and *3 alleles is determined using a polymerase chain reaction–based

microarray. There are no CYP2C19 testing recommendations for PPIs at this time. The sections on clinical pharmacology and drug–drug interactions in the prescription information for esomeprazole, pantoprazole, and rabeprazole have been updated, although no testing is recommended. Professional organizations have been persuaded to issue expert consensus statements as a result of recent reports on PPI usage in patients on antiplatelet therapy. CYP2C19 testing has not yet been established for managing therapy with thienopyridines including PPIs, according to the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association.

1.5.The Functional Effect of the Genomic of Interest

Multiple medications, including neuroleptics, antidepressants, certain beta-blockers, and codeine, are hydroxylated or demethylated by the CYP2D6 enzyme. 60 The CYP2D6 gene is found on chromosome 22, and there are at least 80 known CYP2D6 variations. Factors like CYP2D6 genetic variation might explain the interindividual variability of CYP2D6 enzyme activity. PM, intermediate metabolizer (IM), EM, and ultra-rapid metabolizer are phenotyping subgroups of CYP2D6 genetic variants. The enzyme activity of the EMs is thought to be normal. The morphine metabolite's median AUC rises from PM to EM to UM. The majority of reduced CYP2D6 enzyme activity has been linked to the CYP2D6*3, *4, *5, *6, as well as *7 alleles. Furthermore, the *9 and *10 alleles have been linked to reduced CYP2D6 activity in IMs. In UMs, CYP2D6 gene duplication is linked to greater morphine plasma concentrations and AUCs than in EMs[5].

1.6.Pharmacogenomic Clinical Application Limitations and Challenges:

Pharmacogenomics has the ability to influence clinically important outcomes such as medication dosage, effectiveness, or toxicity, leading to testing recommendations. Pharmacogenomics has not given convincing evidence to need such testing for PPIs and codeine, however. One explanation might be because assessing clinical relevance for some medicines would need consideration of both genetic and nongenetic variables. Determining the amount to which such things contribute is also crucial. Nongenetic variables such as adherence to therapy, antibiotic resistance, and concurrent drug usage, for example, all have an influence on H pylori cure rates and may play a substantial role in illness treatment.

Numerous pharmacogenomic studies with limited sample sizes were undertaken due to the low incidence of a certain variant allele in a studied group. In PPI investigations, homozygous EMs, heterozygous EMs, and PMs were distributed unequally, with a lesser number of PMs. Due to a lack of statistical power, a small sample size is a research design constraint that raises the likelihood of an error. It's possible that the findings of such research aren't reliable. A pharmacogenomic research should ideally have appropriate statistical power, with individuals stratified equally across groups. However, because many variant alleles have a frequency of 1% to 2% in the population, this may not be possible. when evaluating the therapeutic significance of pharmacogenomic research with limited sample numbers, care is advised. Due to difficulties such as a lack of easily available resources, practicality, quality of evidence, and ethical, legal, and societal concerns, integrating pharmacogenomic testing into clinical practice remains a major challenge[6].

1.7. Application of pharmacogenomics:

Pharmacogenomics is developed from the combination of genomics, medical, pharmacological, or biotechnological concepts in order to produce optimal, safe, and efficacious medications with a customized approach based on the genetic differences that exist in all humans, as shown in Figure 1.

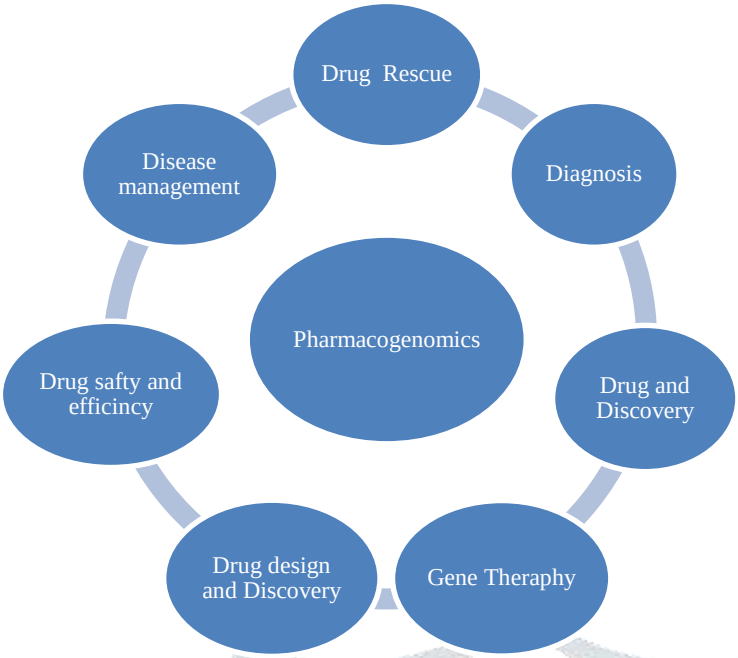

Figure 1: illustrate diagram showing major application of Pharmacogenomics.

1.8.Some Pharmacogenetic Findings That Are Clinically Important:

Pharmacogenetic testing has been used in a variety of therapeutic settings to various degrees. Following is a discussion of a few of these uses**.**

1.8.1. Oncology:

Even among patients with the same kinds and stages of cancer, phenotypic and genetic differences exist. Because many targeted cancer treatments target cell–surface receptors or downstream effector molecules, drug sensitivity and resistance can be influenced by changes in signaling pathway components. One important finding from cancer pharmacogenomic research is that such mutations might help doctors make better treatment decisions and predict patient outcomes. In the last decade, there have also been significant advancements in cancer tissue analysis methods and patient classification. Much of this success has been predicated on the discovery of tumor-specific molecular characteristics. Tests for nonheritable somatic cell DNA mutations are becoming more widely available. The HER2 receptor gene amplification test, which is used to guide trastuzumab treatment for breast cancer, is the most well-known of them (Herceptin, Genentech). HER2 (human epidermal growth factor receptor) is overexpressed in around a quarter of breast cancer patients. Overexpression of the HER2 oncogene has been linked to increased tumor growth and metastasis, as well as a poor prognosis and treatment resistance. Only when a patient has HER-positive cancer, which is defined by very high levels of HER2 protein in the tumor, is trastuzumab evaluated[7].

1.8.2. Cardiology:

Cardiology is the study as well as treatment of heart and blood vascular diseases. A cardiologist may be referred to a patient with heart illness or cardiovascular disease. Internal medicine has a branch called cardiology. A cardiologist and a cardiac surgeon are not the same thing.

In the 1990s, pharmacogenomic research in cardiology lagged, but it has exploded in recent years. Two anti-thrombotic medicines, warfarin and clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-aventis), have made promising discoveries. Dabigatran etexilate mesylate (Pradaxa, Boehringer Ingelheim) was authorized by the FDA in October 2010 as a new anticoagulant agent. Warfarin, acenocoumarol, and phenprocoumon, all oral coumarin anticoagulants (OCAs), have been the mainstay therapy for thromboembolic diseases for more than 60 years[8].

2. LITERATURE REVIEW

Shiew-Mei Huang et al. discussed about application of Pharmacogenomics in Clinical Pharmacology. A patient's reaction to a medication might be influenced by a variety of variables. Extrinsic variables include

smoking, nutrition (food, drink, dietary supplements), and concurrent medicines, as well as intrinsic factors such as age, gender, genetics, race/ethnicity, disease states, organ dysfunctions, and other physiological changes, such as pregnancy and breastfeeding (ICH E5, 1998 and 2004). The risk/benefit ratio for individual individuals might be influenced by the interaction of genotypes of enzymes, transporters, & receptors, as well as other variables (such as concurrent medicines and illness conditions)[9].

Theodora Katsila et al studied about in pharmacogenomics, whole genome sequencing is used. The goal of pharmacogenomics is to learn more about how genes and genetic variations affect clinical treatment response. Although several drug–gene relationships have been identified to date, many obstacles remain in the way of clinical application of pharmacogenomics; treatment trials for pharmacogenomic testing are still in their infancy, while emerging high-throughput genotyping technologies generate a flood of new findings. The impact of whole genome sequencing on pharmacogenomics research and clinical application is discussed in this paper[10].

3. DISCUSSION

Pharmacists are expected to play a key role in preparing health systems including pharmacies for this new area. In order to convert the findings into clinical practice, pharmacists will need to access current pharmacogenomic information. There are a number of evidence-based genomics and/or pharmacogenomics internet resources. Pharmacogenomics is a fast-evolving discipline with substantial therapeutic implications for customizing medicine to enhance effectiveness and/or decrease toxicity. Professional organizations, regulatory agencies, and academics have proposed various, but comparable definitions of pharmacogenetics and pharmacogenomics. The study of genetic origins of individual differences in medication response is referred to as pharmacogenetics. The influence of genetic variants on clinical outcomes is becoming more well recognized. Despite the fact that several studies have found variations in PPI PK and PD variability based on CYP2C19 genotype, there is conflicting data on H pylori eradication rates for the majority of PPIs. Due to substantial supporting evidence between HLA-B*1502 with carbamazepine-induced SJS/TEN, HLA-B*1502 testing is necessary prior to beginning carbamazepine in high-risk individuals.

4. CONCLUSION

There are limitations and obstacles to pharmacogenomic clinical application that must be solved before testing can be implemented in clinical practice. Pharmacogenomics is a rapidly developing discipline that has important therapeutic implications for customizing medications to enhance effectiveness and/or decrease toxicity. Several suggestions have been made by professional groups, regulatory agencies, and scholars, all of which are similar. A qualitative assessment of physician perspectives of pharmacogenomics identified gaps in the present implementation sand recommendations for future development. In particular, pharmacogenomics implementations need to focus on education of both practitioners and patients. Continuous educational outreach may be needed to help with fast speed of knowledge growth. Clinical decision assistance and long-term responsibility for pharmacogenomics panel data are key areas must be addressed by new regulations and new program features. With the increasing use of next generation genotyping of both somatic as well as germline variants, we expect views will shift as more data is produced. Future studies of clinicians' perspectives on genomic medicine should also include a wide range of experts, including those who have already adopted targeted treatment and those who are ready to integrate tailored treatment into their clinical practice. However, there isn't enough evidence to determine whether CYP2D6 polymorphisms influence codeine efficacy as well as toxicity in general. Despite the availability of CYP2C19 or even CYP2D6 genotyping tests, their practical value is limited. Cross product Stevens-Johnson syndrome and toxic epidermal necrolysis are related to the HLA-B*1502 allele (TEN) (TEN). Prior to beginning carbamazepine in high-risk patients, pharmacogenomic testing is required. Several limitations and barriers to implementing pharmacogenomic testing in clinical practice include a lack of resources, provider competency, or ethical, legal, as well as social issues.

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