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A Comprehensive Review on a Potential Tool in Pharmacovigilance – Pharmacogenovigilance

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ABSTRACT

A program called pharmacogenovigilance can be created by incorporating pharmacogenomics into pharmacovigilance research. The pharmacogenomic study of adverse drug reactions (ADRs) is a highly important program since genes are a major factor in the variety of how people react to medications. A patient's susceptibility to rare adverse drug reactions (ADRs) that are not observed in other patients is influenced by genetic differences, which have a major impact on medication activity in many patients. Because of genetic variability, pharmacogenetics offers a more environmentally friendly route to drug safety and efficacy investigations as well as customized medication administration. Pharmacogenovigilance must now be integrated into clinical practice and the public health system in order to investigate these potential benefits. In order to provide his patients with the greatest treatment, a physician must always take genetic factors into account.

INTRODUCTION:

Pharmacogenomics is another name for pharmacogenetics. This area of study examines how a person's genotype influences how they react to drugs. It attempts to customize medical care for each individual or a population. Understanding the efficacy of the medicine and the user's safety while use enhances one's health. Based on an individual's genetic composition, safe drugs may be recommended.[1]

It is a synthesis of genomics, which is the study of genes and their roles, and pharmacology. Although many medications are "one size fits all," not everyone responds to them in the same manner.[3] Therefore, it might be challenging to forecast who will benefit from that medication, who won't respond at all, and who will have adverse drug reactions, which are harmful side effects.[4]

The availability of many new medications has resulted from advancements in drug development technology, which also raises the risk of adverse drug reactions. These have justified the establishment of pharmacovigilance systems, which monitor drug safety. One of the main issues with the pharmacovigilance system is that there is a significant underreporting problem. The field of pharmacogenomics focuses on the investigation of drug-metabolizing enzymes, pharmacogenetics of ADRs, genetic biomarker identification, diagnostic testing for pharmacogenetic decision-making, guidelines for gene/drug pairs, personalized medication use, and drug safety and efficacy studies.[7]

Many affluent nations have embraced pharmacogenomics-based practice; yet, this shift has presented difficulties for medical professionals in their role as suppliers of healthcare services. In order to improve drug safety and efficacy, the primary goals of this article are to evaluate pharmacovigilance concerns about pharmacogenomic biomarkers and to discuss the relationship between pharmacogenetics and pharmacovigilance.

A property of DNA and/or RNA that can be measured and that serves as a marker for pathogenic processes, normal physiological processes, and/or the reaction to therapeutic or other interventions.[5] A biomarker, or biological marker, is defined by the World Health Organisation (WHO) as "any substance, structure, or process that can be measured in the body or its products that influence or predict the incidence of outcome or disease", in collaboration with the United Nations and the International Labour Organisation. A more comprehensive definition considers the results of interventions, therapies, and even accidental

exposure to the environment, including toxins or nutrients. According to the WHO, a real definition of biomarkers is "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological" in their study on the validity of biomarkers in environment risk assessment. While research aims to expand our knowledge of illness causes, there is also optimism that the identification of new risk factors may result in better ways to identify individuals who are either at high risk or in the early stages of the diseases of concern.[9]

Birth of Pharmacogenetics:

Modified drug response may be caused by genetic variables that change the pharmacokinetics and pharmacodynamics of medications. It was discovered in the 1950s that exposure to the antimalarial drug primaquine was the cause of a hereditary shortage of glucose-6-phosphate dehydrogenase, which results in hemolysis.

Vogel first used the word "pharmacogenetics" in 1959. The term "pharmacogenomics" was used in recent years to characterize the gradual realization that a genome is more than the sum of its genes.[17]

Global Scenario in Pharmacovigilance:

Global pharmaceutical product safety is gravitationally dependent on pharmacovigilance, the science and practices of identifying, evaluating, comprehending, and preventing side events or other drug-related issues. An efficient pharmacovigilance system becomes essential in a globalized pharmaceutical business where medications are conceived, produced and supplied internationally.

Globalization and Drug Safety:

The pharmaceutical industry's globalization has boosted cooperation and integrated operations between different locations. This has stepped up the discovery of new pharmaceuticals and increased access to modern therapies, but it has also created new difficulties for global drug safety monitoring and assurance.[20,21]

ADRs are a significant issue for all stakeholders worldwide. ADRs, excluding failure to achieve the intended purpose, are described by the WHO as any adverse and unplanned response to medicine that happens at levels used in people for prevention, diagnosis, or therapy. Following the thalidomide tragedy in the 1960s, an international drug monitoring

programme was established in response to the difficulties healthcare workers encountered with adverse drug reactions. ADRs account for 0.3% to 11% of hospital admissions, which is a substantial number. Drug-related side effects have also been shown to be the fourth most common cause of death in the United States, with a 20% rise in the cost of healthcare attributed to these problems. ADR-related complications can result in both short- and long-term hospital stays, as well as death. About 2 million Americans are hospitalised and 100,000 Americans die as a result of adverse drug reactions (ADRs) each year. ADRs and medication errors are responsible for 2.3% of inpatient admissions in the UK, 4.8% in Germany, and 7.3% in the USA, according to research. According to studies, 20–25% of deaths are related to prescription medicines, and nearly all of these deaths might have been avoided. Up to 50% of recently approved medications were found to have significant adverse drug reactions (ADRs) that were discovered during the post-marketing phase; however, only 5% of these cases were reported. Genetic variables that cause genetic polymorphism, individual variations in an enzyme's capacity to metabolize drugs, and variations in drug receptors and transporters are thought to be the driving forces behind ethnic background. The frequency of adverse drug reactions varies among patient populations as a result of genetic variations.[23]

Collaboration and information sharing:

Cooperation and information sharing play key roles in the global pharmacovigilance scene. Global standards and pharmacovigilance procedures are promoted and harmonized by international organizations like the World Health Organization (WHO) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).[25]

One cooperative effort that enables nations to share data on adverse drug reactions is the WHO Global Individual Case Safety Reports (ICSRs) database. This database makes it easier to identify possible safety issues promptly and to organize a coordinated response to safeguard patient safety.

Harmonization of regulations:

Efforts to harmonize pharmacovigilance regulations and standards are ongoing. The ICH has developed guidelines that aim to standardize the collection, analysis, and reporting of safety data. These guidelines help streamline pharmacovigilance practices across regions, reducing the burden on pharmaceutical companies and regulatory agencies alike.[26]

The role of technology in Pharmacovigilance:

Technological developments have had a big global impact on pharmacovigilance. The utilization of automated data mining, artificial intelligence, and machine learning algorithms is on the rise to more effectively analyze large datasets and detect possible safety signals. By improving pharmacovigilance efforts speed and accuracy through technological integration, safety concerns can be identified early and responded to quickly.[29]

Translating The Hereditary Mosaic - Pharmacogenetics Uncovered:

The field of pharmacogenetics, which studies how a person's genetic makeup influences how they respond to medications, opens up a realm in which a person's unique genetic makeup may be used to help create personalized medicinal interventions. It investigates the genetic variants that influence drug absorption, viability, and anticipated adverse reactions, providing a personalized treatment plan.

Guardians of security - the utmost caution in pharmacy:

The meticulous attention to detail of pharmacovigilance complements the precision of pharmacogenetics. This field focuses on the ongoing review, auditing, and management of prescription security after release. It serves as a defense, ensuring that any unexpected side effects or hostile reactions are promptly identified and addressed, thus preserving public health**.**

Hereditary experiences and accurate perceptions come together in a unique dance created by the collaborative energy of pharmacogenetics and pharmacovigilance. Pharmacogenetics provides an estimate of a person's potential pharmacological response based on their genetic makeup. Pharmacovigilance continues to act as a watchful gatekeeper in the meantime, spotting indications of possible security risks in the broader population.[30]

The commitment of customized security - from hypothesis to practice:

As When cooperative energy unfolds, it becomes clear that there is room for understanding thought to be disturbed. Imagine a healthcare setting where a patient's genetic profile and side effects determine the course of treatment. This personalized strategy increases treatment feasibility and reduces the risk of adverse reactions, providing a positive indication for patients navigating the complexities of medication delivery.

Closing the hole - troubles and imminent skylines:

Although pharmacogenetics and pharmacovigilance are a highly committed relationship, some challenges must be addressed, such as widespread hereditary testing reception and information joining. Looking ahead, there are exciting prospects for advancements in information analysis, innovation, and collaborative efforts to fill up these gaps and unlock this ground-breaking association's full potential.[31]

Safeguarding human subjects:

In pharmacovigilance, obtaining ethical approval is a vital first step in ensuring the safety of human subjects taking part in observational or clinical research. Strict ethical guidelines that cover matters like participant welfare, privacy, and informed consent must be followed.

Informed consent and transparency:

Getting participant's consent is essential to moral pharmacovigilance. By guaranteeing that participants are fully informed of the possible dangers and advantages of their environment, this procedure promotes transparency and builds confidence in the research process.

Beyond the participant level, ethical clearance comprises the security and privacy of the data that is gathered. Considering pharmacovigilance activities manage sensitive patient data, strong security measures are required to prevent data breaches or illegal access.[32,33]

Adherence to regulatory standards:

Research projects and regulatory compliance are connected by ethical approval. Pharmacovigilance operations must adhere to the strongest ethical and legal requirements, as well as recognized frameworks for research to consider the research methods as ethically pure and accountable.

Ethical review boards play a pivotal role in conducting a comprehensive risk-benefit assessment of pharmacovigilance activities. This assessment considers not only the potential benefits of the research but also evaluates and mitigates any foreseeable risks to participants and the border community.

Global perspectives on ethics:

Since pharmacovigilance represents a global field, different nations and regions adhere to distinct ethical standards. Diverse ethical environments must be navigated by researchers, who must also respect and acknowledge cultural differences while maintaining wide ethical standards that put patient welfare first.[35-37]

Ongoing monitoring and research:

There are duties related to ethics that go beyond just starting a study. To ensure that the highest standards are upheld throughout the research process and any emerging ethical concerns are promptly addressed ethical pharmacovigilance requires continuous monitoring and reporting.

Public trust and stakeholder confidence:

Ethical clearance not only safeguards individual participants but also contributes to building public trust and confidence in pharmaceutical research. Upholding ethical standards enhances the credibility of pharmacovigilance efforts, fostering a positive perception among stakeholders.

Challenges and future directions:

There are still obstacles standing in the way of establishing a genuinely worldwide pharmacovigilance system. It is necessary to address obstacles like cultural differences in reporting practices, resource limitations, and disparities in healthcare infrastructure. Emerging technologies also present a unique set of difficulties, such as the need for qualified personnel with the ability to understand complex analytical outputs and worries about data privacy.

Further Evidence:

The best way to safeguard patients is to identify and evaluate ADRs as soon as possible. The variety of drug responses is largely determined by an individual's genetic makeup; yet, advances in pharmacogenomics have significantly increased the safety and effectiveness of drugs. The identification of genetic biomarkers provides more proof that pharmacogenovigilance studies should be included in clinical practice.[38]

Genetic Variables and Biomarkers:

Before drug exposure, genetic biomarkers offer the possibility of predicting drug-related outcomes based on an individual's genetic composition. Biomarker identification has been facilitated by the use of microarray technologies, which have produced results quickly.[39,40] They can be categorized into the following groups according to the impacted parameters:

A. Genetic biomarkers linked to pharmacokinetic and pharmacodynamic processes:

Drug metabolising enzymes (DME) are genetically polymorphic due to variations in gene copy number, including amplification and deletion of genes, minor insertions and deletions, and single-nucleotide polymorphisms (SNPs) in DNA sequence. Individual differences in response to a drug or its metabolites, as well as drug-related issues, are caused by genetic polymorphism, as the majority of phase I and phase II drug metabolising enzymes are polymorphic. The therapeutic significance of genetic variants has been better understood in recent years, and several databases including pharmacogenomic data on drug-metabolizing enzymes are now accessible.

Furthermore, research on the global and local SNP profiles of 283 DMEs and transporter genes from 62 different ethnic groups worldwide revealed that positive selection had occurred on DME gene variation, which adds to the population variability in drug responsiveness. The bulk of pharmacogenetic drug labels pertain to genes encoding phase I and II of DME, and polymorphisms of DME genes are significant drivers of treatment response. Genetic biomarkers recognized by the US FDA were examined and explained. These genetic indicators have affected drug pharmacokinetics and pharmacodynamics by influencing the drug's exposure level or that of its metabolite(s).

Research has been done on the functions of transporter proteins and drug metabolizing enzymes (DME) in relation to drug pharmacokinetics and pharmacodynamics. The use of clopidogrel, a prodrug used to prevent athero-thrombotic events in coronary artery and cerebrovascular disease or after stent implantation, which is metabolised primarily by CYP2C19 to produce the 126 active metabolite that inhibits platelet aggregation, and the post-marketing identification of a PK genomic biomarker with clinical impact on 123 benefit-risk of a medicine have all been studied.

Proton pump inhibitors, for example, are among the 138 CYP2C19 inhibitors with which clopidogrel has been hypothesized to have similar effects. Moreover, the influence of

pharmacogenetic variants on drug pharmacokinetics has been documented, and scientific evidence has been produced in the post-approval stage of the medication life cycle. Another instance of a pharmacodynamic-related genomic variant discovered subsequent to FDA medication approval is the relationship between warfarin use and polymorphisms in the vitamin K epoxide reductase (VKORC1) gene. A review of the ways in which genetic indicators affect pharmacokinetics and pharmacodynamics may be seen in Table 1. In an effort to connect pharmacogenomics with pharmacovigilance, the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and the Canadian Pharmacogenomics Networks for Drug Safety also emphasized such differences in particular guidelines in clinical pharmacology.

Table 1: Summary of Genetic Biomarkers that Affect Pharmacokinetics and Pharmacodynamics

S/N	Biomarkers	Drug name	Clinical outcomes	Types of study
1.	CYP2D6(Various)	Codeine	Non-response/CNS toxicity	GWA
2.	CYP2C9* and *3	Warfarin	Bleeding	GWA
3.	CYP2C19*2, *3, *17	Clopidogrel	S. Thrombosis and Bleeding	GWA
4.	CYP2D6(Various)	Tamoxifen	Breast cancer recurrence	GWA
5.	CYP3A5*3	Tacrolimus	Graft rejection	GWA
6.	CYP2D6(various)	Antidepressants	Non-response	GWA
7.	CYP2C19*17	Escitalopram	Non-response	
8.	CYP2C9*2 and *3	NSAIDs	Gasto-intestinal bleeding	GWA
9.	UGT1A1*28	Irinotecan	Myelotoxicity	GWA
10.	TPMT*2, TPMT*3A, *3C	6-MP and AZA	Myelotoxicity	GWA
11.	CYP2B6	NNRTI	CNS changes	GWA

NSAIDs=Non-Steroidal Anti-Inflammatory Drug, **NNRTI**=Non-Nucleoside Reverse Transcriptase Inhibitors

Table 2. Genetic Biomarkers that are Associated with Drug-Induced Toxicity Risk Status

No.	Biomarkers	Drug name	Clinical outcomes	Types of study
1.	B*57:01	Abacavir	Hypersensitivity	Candidate gene
2.	DRB1*15:01-DQB1*06:02 A*02:01	Amoxy-clavlnate	Liver injury	Candidate gene
3.	DRB1*07*01-DQA*02:01	Ximelagatran	Liver injury	GWA
4.	A*33:03	Ticlopidine	Liver injury	GWA
5.	B*57:01	Flucloxacillin	Liver injury	GWA
6.	DRB1*15:01-DQB1*06:02	Limiracoxib	Liver injury	GWA
7.	DQA1*02:01	Lapatinib	Liver injury	GW and Candidate
8.	DRB1*01	Nevirapine	Liver injury	Candidate gene
9	B*15:02	Carbamazepine	SJS and TEN	Candidate gene
10	A*31:01	Carbamazepine	Various skin reactions	GWA
11	B*58:01	Allopurinol	Various skin reactions	Candidate gene
12	B*35:05	Nevirapine	Skin reactions	GW and Candidate
13	Cw*8	Nevirapine	Skin reactions	GW and Candidate
14	Cw*04	Nevirapine	Skin reactions	Candidate gene
15	CYP2B6	Carbamazepine	Skin rashes	Candidate gene
16	NAT2	Isoniazid	DI Liver injury	Candidate gene
17	UGT1A	Tolcapone	DI Liver injury	Candidate gene
18	UGT2B7	Diclofenac	DI Liver injury	Candidate gene
19	UGT1A	Various drug	DI Liver injury	GWA
20	IL4, C-590A	Diclofenac	DI Liver injury	Candidate gene
21	IL6, intron	Tacrine	DI Liver injury	Candidate gene
22	IL10, C-627A	Diclofenac	DI Liver injury	Candidate gene
23	UGT1A6*4	Diclofenac	Cardiac toxicity and HF	
24	NOS3 rS1799983	Vincristine	Neurotoxicity	
25	TPMT	Cisplatine	Ototoxicity, Neurotoxicity and Nephrotoxicity	
26	SLCO1B1	Simvastatin	Myopathy	GWA
27	ABCB11	Various drugs	DI Liver injury	Candidate gene
28	ABCC2	Diclofenac	DI Liver injury	Candidate gene
29	SLC22A1(OCT1)	Metformin,Opoid, and odensetron	Hepatotoxicity	Candidate gene
30	SLCC28A3	Anthracycline	Cardiotoxicity	

DI=Drug-Induced, **SJS**= Steven Johnson Syndrome, **TEN**=Toxic Epidermal Necrosis

B. Genetic Biomarkers Independent of Pharmacokinetic and Pharmacodynamic Effects:

These are severe side effects of medication that were brought on by toxicity. Drug exposure can have several undesirable and dangerous side effects, some of which are dependent on the

patient's risk status and genetic biomarkers. Human Leukocyte Antigen (HLA) has been shown over the course of three decades to be a risk predictor for a number of adverse drug reactions (ADRs), which are classified as follows:

1. Genetic marker linked to liver damage caused by drugs:

Human leukocyte antigen (HLA) genes play a role in the development of major adverse drug reactions (ADRs) in vulnerable persons in many current drugs. The first reports of a connection between HLA and genetic susceptibility for drug-induced liver injury (DILI) concerned the use of halothane, an anesthetic that was commonly used until the 1980s and was a major cause of idiosyncratic hepatitis. A study conducted in Japan found a relationship between the HLA class II serotype DR2. Class I serotype HLA-A11 was linked to DILI caused by tricyclic antidepressants and Diclofenac in a comprehensive investigation involving numerous medications, while class II serotype HLA-DR6 was linked to DILI caused by chlorpromazine.

Rather than relying on serotype identification, HLA correlations with DILI have more recently been directly investigated by genotyping. Gene connection with amoxicillin-clavulanate-related DILI was the first HLA genotyping investigation. Even though this type of DILI typically lacks characteristics associated with the traditional immune system, two separate gene association studies found an identical connection with the HLADRB1*15:01 allele, which is associated with a particular DR2 serotype. In a similar vein, the drug's clavulanic acid component was mostly linked to this type of DILI. Numerous distinct HLA class I and II connections have been found as a consequence of further genetic research on DILI that used both candidate gene and GWA techniques (Table 2).[42]

2. Genetic markers linked to skin-related hypersensitivity reactions:

The two categories of serious adverse drug reactions (ADRs) that affect the skin and involve drug-induced hypersensitivity are HLA genetic associated and non-HLA genetic associated. A recent study revealed the involvement of T-cell reactions in drug-induced skin rash and the observed HLA correlations with this reaction. In Taiwanese cases of carbamazepine-induced SJS, a candidate gene research that included genotyping for HLA alleles and a variety of polymorphisms in cytochromes P450 discovered a very substantial correlation between the class I allele B*15:02 and adverse drug reaction (Table 2). Before prescribing carbamazepine, it is now advised to genotype for B*15:02 in people of Han Chinese, Thai, Malaysian,

Indonesian, Philippine, and South Indian ethnicities. However, most other ethnic groups do not show this association, most likely due to the low frequency of B*15:02 in these populations. It doesn't seem that the HLA allele B*15:02 increases the likelihood of more frequent, moderate cutaneous responses brought on by carbamazepine. Numerous HLA correlations with ADRs affecting skin have been found as a result of a combination of candidate genes and GWA studies. The most recent information on genetic indicators linked to inert immunity, cardiac toxicity, and other peculiar medication reactions is compiled in Table 2.[44]

Limitations:

Many articles were included in this study but some of the full texts were not accessible. Due to continuous research in the field of pharmacogenomics and pharmacovigilance this articles covers limited number of biomarkers within its scope and due to time factor.

Conclusion:

Pharmacogenomics is a key factor in optimizing medication safety, whereas pharmacovigilance improves patient care and safety and helps public health initiatives. Despite the significant responsibilities that pharmacogenomics plays in guaranteeing medication safety and the established nature of pharmacovigilance centers, pharmacogenomics was mistakenly viewed as an expensive field that received inadequate support from governments, particularly in developing nations. Under the current pharmacovigilance system, medical professionals identify and report side effects associated with long-established medications without taking into account the genetic diversity in a patient's drug response. Since it has been shown that no medication is suitable for everyone, it is now required to assess and track medications using unique genetic indicators. Pharmacogenomics has not yet been included into pharmacovigilance since, generally speaking, it is not seen as a crucial instrument for medication safety. This is caused by healthcare providers' lack of knowledge and awareness as well as their misinterpretation of the purposes and meaning of the two disciplines. Ultimately, if the topic of pharmacogenomics is adequately explored, the advancements gained in this field will greatly aid in the resolution of drug-related issues. Since 134 nations were a part of the WHO pharmacovigilance program as of the end of 2010, combining pharmacogenomics with pharmacovigilance studies would be the quickest and easiest way to close the current

knowledge and awareness gap and successfully integrate pharmacogenomics into public health.

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