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"PHARMACOGENOMICS CURRENT SCENARIO: CLINICAL APPLICATIONS AND CHALLENGES"

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ABSTRACT

Variability in Drug response is major and one of the most important Challenges faced by the Clinicians in todays' practice. Adverse Drug reactions contribute significantly in Mortality and Morbidity all over the world. Most of these can be avoided by means of applications of Pharmacogenomics. Clinical Applications of Pharmacogenomics have helped Clinicians to replace traditional drug regimens to more safe and customized drug regimens. Pharmacogenomics applications are also seen in research at earlier stages of drug trials for development of more targeted drugs. This article aims at providing an update about information on pharmacogenomics' current applications in clinical medicine and also informs about the Pharmacogenetics of certain Idiosyncratic Adverse Drug Reactions so far proved. This article introduces the Concept of Individualized medicine endorsing more Customized Rational Use of drugs as well as discusses the Current challenges in Implementation of Pharmacogenomics in clinical practice as well in Research.

KEYPOINTS: Pharmacogenomics; Individualized medicine; Variability in Drug response; Adverse Drug Reactions; Rational use of drugs.

INTRODUCTION

"*If it were not for the great variability among individuals, medicine might as well be a science and not an art"* ----Sir William Osler.

We come across many frequently asked questions from patients side in day to day clinical practice like "Why do we respond to the same medications and doses differently??!!" or "Why the side effects we experience are the different for the same medications??!!" This

variability is due to many factors and important one being - One's inherited genes from unique genetic make-up.

Individual variability in Drug Efficacy and Drug Safety reflecting to variable treatment responses is a Major Challenge in Current Clinical Practice, Drug Regulation and Drug Development.[1] Due to realization of multifactorial controls of genetic variations for Drug response; convergence of pharmacogenetics (which is a study of role of Inheritance in Individual variation in Drug response)[2] with Human Genomics gave birth to *Pharmacogenomics* which is an overall study of the many various genes that contribute to drug response.[3] Variability in Drug response which ranges from potentially life threatening Adverse Drug Reactions to equally serious lack of Therapeutic Efficacy can be managed through the application known as Pharmacogenomics.[4]

Considering genomic markers at the Research stage of drug discovery ensures development of effective as well as safe medications with their doses tailored as per the person's genetic make-up.[5] This lays the foundation of the *Individualized medicine*. By the virtue of Advances in Technology and Genomics Pharmacogenomics has a huge potential for applications at Research and Development of Drugs with many of them under consideration.[6]

However there are many Challenges that are encountered with the Process of Implementing the Applications of Pharmacogenomics in clinical practice and Research development process. [7]

PHARMACOGENOMICS IN CLINICAL PRACTICE: A NECESSARY REQUISITE

There are many domains when it comes to describe the need for the Application of Pharmacogenomics in Clinical Practice some of them can be very well be encountered.

1. A patient with complains of inadequate Pain control despite the dose of the Analgesic being well within Therapeutic range; exemplified for Therapeutic Inefficacy.
2. A patient presenting with signs of Drug toxicity; on prescription of the drug after taking the therapeutically calculated dose.
3. Drug Resistance: An evolving major issue considering Antimicrobial Drugs.
4. Hypersensitivity after initiation of Drug therapy

5. Multidrug regimen as a Chronic therapy generally show Non-compliance due to Non personalised interventions as well as cost issues due to Trial and error ways of prescription (Anti-microbial drugs etc.).[8]

CURRENT CLINICAL APPLICATIONS OF PHARMACOGENOMICS

Pharmacogenomics is successfully translated in the field of Oncology and has many other applications of genomic markers in drug classes like Anti-diabetic drugs (Metformin); Analgesics (Opioids-Codeine); Antiplatelet Agents (Clopidogrel); Anticoagulants (Warfarin); Anti-Epileptic drugs (Carbamazepine). Also There are various genotypes that have effect on the extent of drug interactions (E.g. Metoprolol (CYP2D6) and Diphenhydramine). [7] These are applied to avoid the serious outcomes of drug interactions.

Metformin Pharmacogentics[9, 10, 11]

- Incidence of Type 2 Diabetes Mellitus has increased and Metformin remains the most widely used first line pharmacotherapy for its treatment; however marked inter-individual variability in response reduces its optimal use.
- Metformin acts as an Insulin sensitizer drug from the group of Biguanide Oral hypoglycaemic drugs and about 35% of patients fail to achieve initial glycaemic control on metformin monotherapy.
- Distinct mechanisms may underlie failure of Metformin efficacy, both of which are likely to be multifactorial.
- Variants in *SLC22A1* gene coding for OCT 1 can cause reduced Metformin response in initial lowering of HbA1C
- Also Variants in *SLC47A1* coding for MATE1 show Increased metformin response to HbA1C; while variants in gene *SLC47A2* for MATE2 show poorer response to metformin.
- Variants of ATM gene (ataxia telangiectasia mutated gene) at Chromosome 11 involved in Metformin's activation by AMPK (AMP activated protein kinase) involved in Treatment success with Metformin Monotherapy.

Warfarin Pharmacogenetics[12, 13,18]

- Warfarin's direct target protein-- Vitamin K Epoxide Reductase complex subunit 1 *(VKORC1).*

- VKOR catalyses conversion of Vitamin K epoxide to reduced vitamin K required for factors II, VII, IX and X.
- Inhibition of VKORC1 by Warfarin causes depletion of reduced Vitamin K and, consequently, production of hypo-functional coagulation factors resulting in anticoagulation. (phenotype)
- Most VKORC1 polymorphisms are in Regulatory regions of gene and influence warfarin dose across the normal dosing range.
- *CYP2C9 genetic variations* also affect Warfarin dosages.

Clopidogrel Pharmacogenetics[13, 14, 15,18]

- Clopidogrel is most commonly prescribed Oral anti platelet drug in cardiology practice. However there is significant interpatient variability in clinical response to Clopidogrel, which is due in part to genetic variability.
- As the consequences of reduced Clopidogrel effectiveness, namely adverse cardiovascular events can be life threatening and costly makes it primary target of pharmacogenetics intervention.
- There is a strong association between CYP2C19 genotype, and Clopidogrel activation; Clopidogrel is prescribed as a Prodrug attributing to its effectiveness.
- CYP2C19 loss of function allele, the most common of which is the *CYP2C19*2* allele, responsible for the failed activation of the drug into active metabolite.
- Intermediate metabolizers (IMs) with one *loss-of-function allele* and poor metabolizers (PMs) with two loss-of-function alleles have a lower plasma concentration of the active thiol metabolite, as well as decreased inhibition of ADP-induced platelet aggregation.
- There is also a common *gain-of-function allele*, *CYP2C19*17*, with some evidence of its association with enhanced Clopidogrel effects and increased bleeding risk with Clopidogrel (data is not sufficient)
- A boxed warning was added to the US FDA approved Clopidogrel labelling in 2010 in response to data demonstrating reduced Clopidogrel efficacy based on genotype but guidelines do not recommend alternative antiplatelet therapy based on the *17 allele alone (genotype with enhanced Clopidogrel function).

Codeine Analgesia in Children[16]

- Codeine Analgesia is wholly due to its conversion to Morphine by CYP2D6 Cytochrome P450 Enzyme.
- Over 50 different genetic variants are known to exist for *CYP2D6*, which leads to a wide spectrum of metabolic capabilities among the Paediatric Population.
- In simple words, Individuals are normally classified as either poor metabolizers (PM) or extensive metabolizers (EM), depending on the activity of the enzyme.
- Hence Variants of *CYP2D6* affect the dose and therapeutic efficacy of Codeine in Children.

Carbamazepine Pharmacogenetics[17]

- Carbamazepine is an anticonvulsant drug widely used for the indications like Epilepsy and other seizure disorders, bipolar disorders and Drug of choice of Trigeminal Neuralgia.
- HLA-B gene located on chromosome 6 is a part of the Class I complex and belongs to Major Histocompatibility Complex; responsible for the immune response against Non Self antigens.
- Variant allele *HLA-B*15:02* is associated with an increased risk of Carbamazepine induced Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) This genetic variant is specific only to these adverse effects and not the other cutaneous adverse reactions.
- As per FDA recommendations on Carbamazepine Treatment, Genetic testing for HLA-B*15:02 is to be done. Non carriers of HLA-B*15:02 have normal or reduced risk of Carbamazepine induced SJS and TEN in which the drug can be prescribed normally whereas Carriers of HLA-B*15:02 have increased risk of Carbamazepine induced SJS and TEN and hence a different agent needs to be used depending on the underlying disease. The drug can be continued if it was prescribed in past for more than 3 months without incidences of SJS and TEN but will be optional as per the treating physician.

PHARMACOGENOMIC TOOLS IN CANCER THERAPY[19, 20, 21, 22,23, 24]

Oncology is a field with emerging applications of Pharmacogenetics and pharmacogenomics serving as tools to elucidate the genetic bases for inter individual drug response and the development of biomarkers affecting drug responses. These individualised implementations

facilitate more targeted therapies leading to more successful outcomes and also avoid the chemotherapeutic toxicities.[20]

Considering the significant heterogeneity associated with patient responses to anticancer agents and their narrow therapeutic index, Enhanced understanding of cancer genetics has great potential to offer individualized oncologic treatment regimens. Currently 300 metabolic enzymes are under genes and molecules have been subjected to PG investigations and clinical applications.[20, 21,22]

Now a days Tumour profiling and considering genomic biomarkers while planning regimens for Cancers help Chemotherapy to be more targeted.[24] There examples enlisted below:

1. Tumour Profiling of Breast Cancer with the help of Estrogen or HER2 receptors has personalised treatment regimens as well as improved success rates of the therapies.[22]
2. With the increase of incidence of Colorectal Cancer Pharmacogenomic biomarkers for Colorectal Cancer are gaining more attention. *KRAS* Mutation and polymorphisms in EGFR gene are main biomarkers to be considered while planning the Metastatic Colorectal Cancer treatment regimens.[23]
3. Oncogene *BRAF* is the most frequently mutated protein in melanoma. With this consideration there has been development of personalized and more targeted Drug regimens for Metastatic Melanoma.
4. Whole-genome sequencing and whole-exome sequencing studies in Chronic Lymphocytic Leukaemia patients have identified recurrently mutated genes such as *NOTCH-1*, *SF3B1*, *TP53*, *BIRC-3*, and *POT-1* which are considered while planning the regimens. Chronic Myeloid Leukaemia has specific markers like presence of Philadelphia Chromosome and BCR-ABL fusion gene.

Examples of Anti-Cancer drugs with Pharmacogenomics Recommendations[21]

GENE/MARKER	DRUGS	INDICATION
ALK (Anaplastic Lymphoma Kinase)	Crizotinib	ALK positive Non-Small Cell Lung Cancer (Ca)
BRAF	Vemurafenib, Trametinib	Metastatic Melanoma
BRAF, G6PD	Dabrafenib	Same as above
BCR/ABL1	Homoharringtonine Omacetaxine	Chronic Myeloid Leukaemia (CML).
BCR/ABL1, KIT , PDGFBR	Imatinib	CML
BCR/ABL1 Philadelphia Chromosome	Bosutinib	Same as above
Same as above	Dasatinib	CML and Phil. Chromosome

		positive ALL
Philadelphia Chromosome, UGT1A1	Nilotinib	CML
CD30	Brentuximab Vedotin	Hodgkin Lymphoma & Anaplastic large Cell Lymphoma
DPYD gene encoding Dihydropyrimidine dehydrogenase (DPD)	Capecitabine	Metastatic Colorectal Ca Metastatic Breast Ca
Same as above	5-Fluorouracil	Stomach & Colorectal Ca; Pancreatic Ca, Breast Ca
EGFR	Afatinib, Erlotinib	Metastatic Non-small cell Lung Ca
EGFR, KRAS	Cetuximab, Panitumumab,	EGFR expressing Colorectal Ca
EGFR, CYP2D6	Gefitinib	Metastatic Non-small cell Lung Ca
ERBB 2 or HER-2/Neu	Lapatinib, Transtuzumab	Hormone receptor positive Metastatic Breast Ca
ERBB2, ESR1	Everolimus	For HER2 negative Breast Ca, Neuroendocrine tumours of pancreatic origin (PNET), Advanced Renal Cell Ca
ESR1	Exemestane	ER positive early Breast Ca
ESR1, PGR,F2,F5	Tamoxifen	ER positive Breast Ca
ESR1, PGR	Letrozole	Same as above
MS4A1	Rituximab	Non Hodgkin Lymphoma
Same as above	Ibritumomab	Radio immunotherapy of B cell Non Hodgkin Lymphoma
TPMT	Mercaptopurine	Acute lymphoblastic Leukaemia
Same as above	Azathioprine	As an Immunosuppressant in Renal Transplantation
Same as above	Cisplatin	Metastatic Testicular and Ovarian tumours
UGT1A1	Irinotecan	Metastatic Colorectal Ca
Same as above	Pazopanib	Advanced Soft Tissue Sarcoma

There are so many current programs that use pre-emptive genotyping to optimize the pharmacotherapy of, patients US[25] as well as at some Institutes in India. Hospitals and Research Centres in India like AIIMS, JIPMER (ICMR centre) and KEM[14], Mumbai have ongoing projects of Pharmacogenetic Applications alongside the Therapeutic Drug Monitoring OPDs.

Drugs currently under the lens are drugs for epilepsy, Diabetes (Metformin), cancer, stroke, heart disease (Clopidogrel) or deep vein thrombosis (Warfarin).[26]

PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS[4]

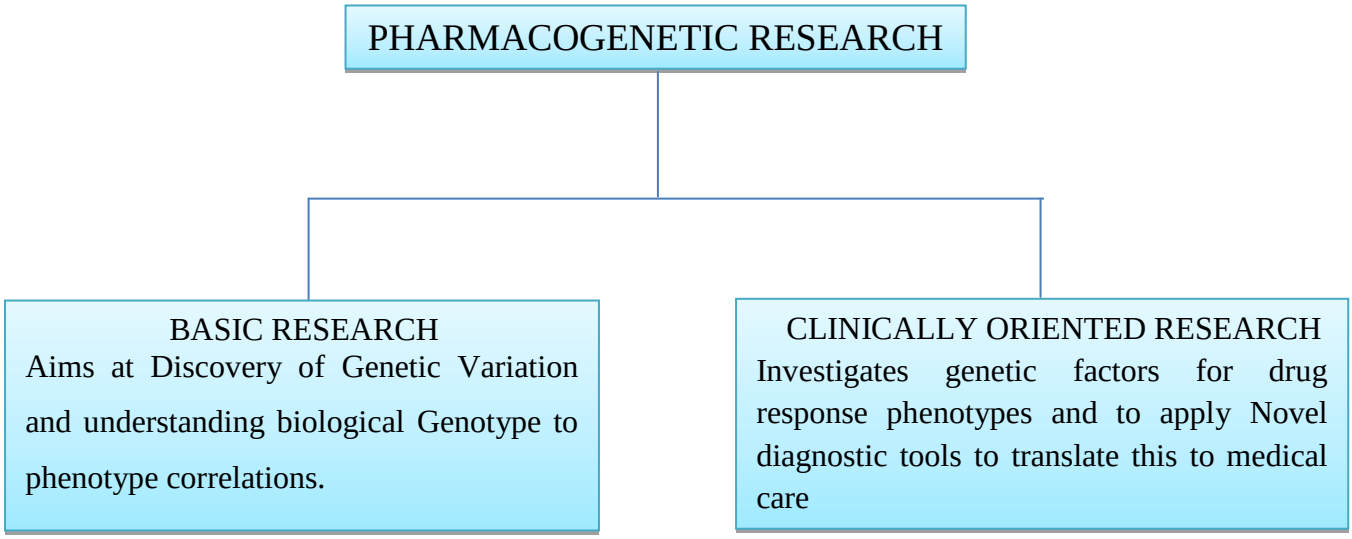
Considerable progress has been made in identifying genetic risk factors for idiosyncratic adverse drug reactions in the past 30 years. Using both candidate gene and Genome-wide association studies (GWAS); various genes that make contributions of varying extents to these reactions have been identified. Many of the associations identified for reactions affecting the liver and skin involve human leukocyte antigen (HLA) genes and for reactions relating to the drugs Abacavir and Carbamazepine, HLA genotyping is now in routine use prior to drug prescription. Progress on non-HLA genes affecting adverse drug reactions has been less, but some important associations are considered. Some Examples are given below.

DRUG	REACTION/ TOXICITY	GENE/ HLA ALLELE
Abacavir	Hypersensitivity	B*57:01
Allopurinol	Various skin reactions incl. SJS, TEN	B*58:01
Amoxicillin-Clavulanate	Liver injury	DRB1*15:01- DQB1*06:02 A*02:01
Carbamazepine	SJS And TEN Various skin reactions like SJS and TEN	B*15:02 A*31:01
Ticlopidine	Liver injury	A*33:03
Nevirapine	Liver injury	DRB1*01
	Various skin reactions	B*35:05
	Skin rash	CYP2B6
Isoniazid	Drug Induced Liver injury	NAT 2
Diclofenac	Drug Induced Liver injury	ABCC2, UGT2B7
Simvastatin	Myopathy	SLCO1B1

In addition to these there are a number of other relatively common reactions, including Clozapine-induced agranulocytosis, Bisphosphonate-induced osteonecrosis of the jaw (BONJ) and renal toxicity, that are important clinical problems. Clozapine-induced agranulocytosis has recently been shown to be HLA-associated and some genetic risk factors for BONJ have also been described.

RESEARCH TRENDS IN PHARMACOGENOMICS IN INDIA[27,28]

For the Pharmacogenetic research the major functional variants of each gene is a precondition for developing diagnostic tools, select relevant variants for Pharmacogenetic studies and to correctly interpret associations in research.



First human genome sequencing as part of Human Genome (HUGO) project in India, IGIB New Delhi, is a step closer towards personalized medicine. CSIR led Indian Genome Variation (IGV) project studied 1,000 bio medically important and pharmaco-genetically relevant genes, in genetic spectrum of India.

Current Challenges faced in Research[28]

- Genetic alterations in gene expression at multiple effects at multiple levels--**The rule rather than Exception!!**
- Patients are often treated with combinations of drugs often complicates the basic research stream of pharmacogenetics research.
- Other influential factors like Non genetic; Environmental factors and the circadian rhythms affect the Phenotype expression Hence, Multifactorial basis of phenotype expression complicates research methods.
- Lack of abundant In vitro test Systems.
- Cost of the studies is usually higher as the genetic tests are expensive. Also the Cost for maintaining the required infra structure and Quality Standardization of the labs.
- Lack of collaborative Biobanks and thus lack of extensive medical sample information.

PHARMACOGENOMICS AND DRUG DEVELOPMENT[27, 28,29]

Pharmacogenomics serves as a great tool in clinical Trials of the Drug Development field.[27]

Phases of clinical Trials	Benefits of Pharmacogenetics
Phase I	Refinement of phase I studies by focusing on known genotypes from preclinical testing Early detection of problems with compound (Reduces the cost)
Phase II	Further Refinement of determinants of drug response provides data for design of Phase III
Phase III	Reduction of Studies & sample size ; re-evaluation of phases I&II
Phase IV	Drug is Licensed and FDA

Although the field of Pharmacogenetics has existed for decades, the implementation of, Pharmacogenetic testing for the application of Pharmacogenomics in clinical practice has been slow in India. However, gradual inclusion of Pharmacogenomic studies in drug discovery and development will cause substantial reduction in the expenses involved in drug development, ensure a safe clinical trial and reduce failures.

CRITICAL ISSUES IN IMPLEMENTATION OF PHARMACOGENOMICS IN CLINICS[30]

- There are only 17 of ~ 18,000 human genes that are considered clinically actionable for germline pharmacogenomics.
- Lack of Awareness among Physicians about Pharmacogenetics of the commonly prescribed drugs as well as about genetic variant specific adverse drug reactions.
- Lack of guidance for how to interpret Pharmacogenetic tests data in the clinics before starting the drug
- Poor accessibility and availability of the Genetic testing.

If genetic testing were more widely and appropriately deployed clinically; prescribing could be improved and outcomes optimized for that relatively small set of medications for which genomics is actionable

- Lack of adequate number of Institutions and Highly advanced and equipped labs to process the Genetic tests.
- Lack of Standardization of the Genetic results all over the Country.
- Due to Higher Cost of the Genetic Tests; these are not always affordable by patients.
- Concerns about costs and reimbursement by Insurance companies.

- Lack of Awareness among patients about benefits of pharmacogenomics applications and personalized medicine.
- Deficit of support systems and infrastructure to handle and store large amounts of genomic data.
- Lack of Nationwide Network providing necessary information about implementations like guidelines and recommendations which can be accessed by the Clinicians all over the country along with the new updates from the Pharmacogenomic Research field.

DISCUSSION

There are successful implementations of Pharmacogenomics in Clinical practice so far, and FDA-mandated incorporation of Pharmacogenomic information in drug labelling will remain an important step in the acceptance of pharmacogenomics in clinical practice.

As mentioned above there are many hurdles to overcome at field as well as at Drug development and Research level. However, as the evidenced supporting, Pharmacogenomic testing continues to grow, the momentum for clinical implementation of pharmacogenomics should accelerate. Also Pharmacogenetic testing in combination with other inventions may serve to improve medical adherence.

Going forward, is a growing body of evidence that pharmacogenomics will be an expanding component of evidence-based precision medicine. It can lead to a future with Individualised Medicine where there is more rational use of drugs with customized drug regimens leading to much lesser adverse drug reactions.

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