Pharmacogenomics and its Usage in Clinical Settings

Atul Thatai[1*]

[1]Department of Molecular Laboratory and Cytogenomics
Max Super Speciality Hospital, Saket, New Delhi

Correspondence:

Atul Thatai

E-mail: atul.thatai@maxhealthcare.com

Definition

Pharmacogenomics is the study of how an individual's genetic makeup influences their response to drugs. It involves analysing the interplay between an individual's genetic variations and their response to medications, aiming to personalise drug treatment for enhanced efficacy and reduced adverse effects.

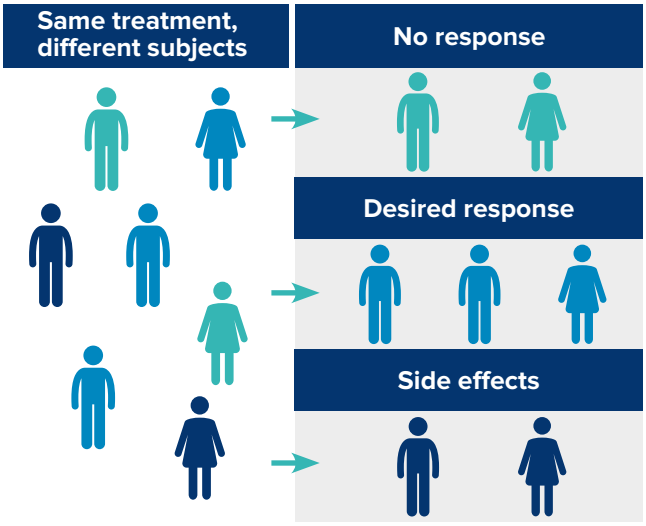

Figure 1: Effect of drug on different subjects

Significance

a. **Personalised medicine:** Pharmacogenomics facilitates the tailoring of drug treatments based on an individual's genetic profile, leading to more effective and personalised medical interventions.

b. **Optimising drug efficacy:** Understanding genetic variations helps identify patients who may require different drug dosages or alternative medications to achieve optimal therapeutic outcomes.

c. **Minimising adverse drug reactions:** By considering genetic factors, healthcare providers can predict and prevent adverse drug reactions, improving patient safety.

d. **Treatment decision support:** Pharmacogenomic data can serve as a valuable tool for healthcare providers in making informed decisions about drug selection and dosage adjustments.

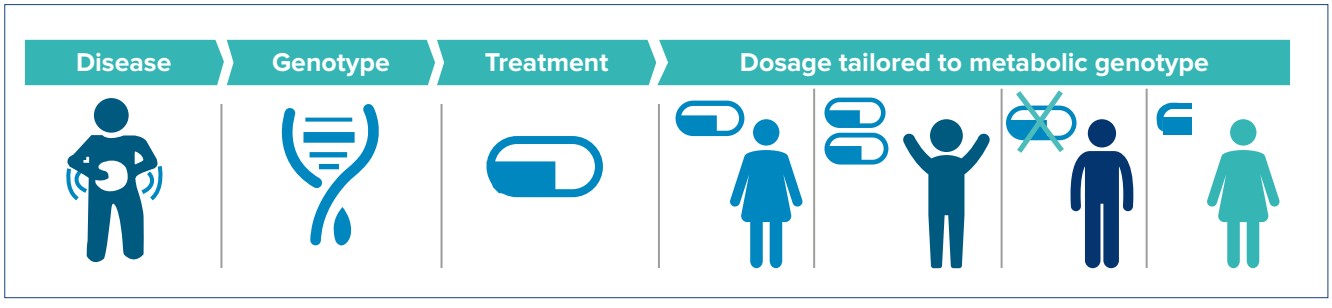

Figure 2: Pharmacogenomics can help tailor treatment and dosage requirements

Challenges

- Limited Evidence for All Drugs: Comprehensive pharmacogenomic data is not available for all drugs, making it challenging to implement personalized medicine across all medical conditions.
- Inter-individual Variability: Individuals may respond differently to drugs, and other factors such as environmental influences and drug-drug interactions also play a role.
- Integration into Clinical Practice: The integration of pharmacogenomics into routine clinical practice faces challenges, including the need for standardized guidelines, education for healthcare professionals, and infrastructure for genetic testing.
- Ethical and Privacy Concerns: The use of genetic information raises ethical concerns related to informed consent, privacy, and potential misuse of sensitive data.

Guidelines from CPIC and FDA

Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Provides evidence-based guidelines for specific gene-drug pairs.
- Classifies recommendations based on the strength of evidence.
- Regularly update guidelines to incorporate new evidence.

U.S. Food and Drug Administration (FDA)

- Requires drug manufacturers to include pharmacogenomic information in drug labels when relevant.
- Encourages consideration of pharmacogenomic data in drug development.
- Collaborates with organisations like CPIC to ensure consistency in translating pharmacogenomic information into clinical practice.

Considerations for implementation of a pharmacogenomics programme

- **Pre-emptive Genetic Testing:** Consider genetic testing before prescribing certain drugs for personalised treatment.
- **Communication and Education:** Educate healthcare professionals and patients about the role of genetics in drug response.
- **Integration into EHR and CDSS:** Integrate pharmacogenomic data into electronic health records and implement clinical decision support systems.
- **Continued Research and Updates:** Stay informed about the latest research and updates in pharmacogenomics.
- **Collaboration and Interdisciplinary Care:** Foster collaboration among healthcare professionals for comprehensive patient care.
- **Patient Consent and Privacy:** Obtain informed consent for genetic testing and ensure patient privacy.
- **Post-Marketing Surveillance:** Continuously monitor patients for drug efficacy and adverse effects.
- **Education for Patients:** Encourage patient understanding and involvement in healthcare decisions.

Some examples of pharmacogenomics

S.no.	Drug name	Drug type	Gene	Clinical relevance/CPIC guidelines
1	Warfarin	Anticoagulant	CYP2C9, VKORC1	CPIC provides recommendations for warfarin dosing based on CYP2C9 and VKORC1 genotypes, ensuring optimal anticoagulation with minimized bleeding risk.
2	Clopidogrel	Antiplatelet	CYP2C19	CPIC offers guidance on antiplatelet therapy with clopidogrel based on CYP2C19 genotypes, suggesting alternative medications or adjusted dosages.
3	Codeine	Pain Relief	CYP2D6	CPIC provides recommendations for codeine therapy based on CYP2D6 genotypes. Poor metabolizers may require alternative pain medications to avoid inadequate relief.
4	Abacavir	Antiretroviral for HIV	HLA-B*5701	CPIC recommends HLA-B*5701 testing before abacavir therapy, as positive individuals are at an increased risk of hypersensitivity reactions.
5	Tamoxifen	Breast Cancer Treatment	CYP2D6	CPIC provides guidance on tamoxifen therapy based on CYP2D6 genotypes, considering the impact on drug metabolism and efficacy.

S.no.	Drug name	Drug type	Gene	Clinical relevance/CPIC guidelines
6	Tacrolimus	Immunosuppressant	CYP3A5, CYP3A4	CPIC provides recommendations for tacrolimus dosing based on CYP3A5 and CYP3A4 genotypes to optimize immunosuppression after organ transplantation.
7	Fluoropyrimidines	5-Fluorouracil, Capecitabine	DPD (Dihydropyrimidine Dehydrogenase)	Individuals with DPD deficiency may experience severe toxicity with fluoropyrimidine chemotherapy. Dosing adjustments or alternative therapies are warranted.
8	Irinotecan	Anticancer Agent	UGT1A1 (UDP Glucuronosyltransferase 1A1)	CPIC provides guidelines for adjusting irinotecan dosages based on UGT1A1 genotypes to manage toxicity.
9	Azathioprine	Thiopurines	TPMT (Thiopurine S-Methyltransferase)	TPMT genotyping helps guide the dosing of thiopurines, preventing excessive myelosuppression in individuals with low TPMT activity.
10	Mercaptopurine	Thiopurines	NUDT15	NUDT15 genotyping aids in determining optimal dosages for thiopurines, reducing the risk of hematologic toxicity.

Reports can be generated for a particular drug, a particular class of drug, or a comprehensive report covering all major drugs.

Test Requested: UGT1A1 GENE POLYMORHISM

Method Used

PCR, Fragment Analysis

Results

TA Repeats	UGT1A1 Genotype
7/7	UGT1A1*28/*28

Interpretation

TA Repeats	UGT1A1 Genotype	Remarks
Nomenclature	Recommendation	
UGT1A1*1/1	6/6 Recommendation: Normal Dosage Indicated	Patients who are homozygous for 6 thymine-adenine (TA) repeats demonstrate full enzyme activity and are associated with minimal toxicity with standard Irinotecan dosage. It is the wild-type allele associated with normal enzyme activity.
UGT1A1*1/*28	6/7 Recommendation: Increase risk of Neutropenia	This allele represents 7 thymine-adenine (TA) repeats within the promoter region as opposed to 6 that characterizes the wild-type allele. It leads to impairment of gene transcription and a decrease in transcriptional activity by approximately 70%. Patients who carry this genotype in UGT1A1 are at increased risk for neutropenia following initiation of irinotecan treatment.
UGT1A1*28/-28	7/7 Recommendation: Increase risk of Bone marrow toxicity. Associated with Gilbert Syndrome	Patients with 7 thymine-adenine (TA) repeat (7/7 homozygous) demonstrate severely reduced glucuronidation activity. The presence of this genotype in UGT1A1 may indicate an increased risk of bone marrow toxicity when treated with irinotecan.
UGT1A1-28/-37	7/8 Recommendation: Increase risk of Neutropenia	Patients with 7 thymine-adenine (TA) repeats in one allele and one 8 thymine-adenine (TA) repeats in other allele (7/8 heterozygous) demonstrate reduced transcription rate and a lower enzyme level.
UGT1A1-37/-37	8/8 Recommendation: Increase risk of Neutropenia	Patient with (UGT1A1 37, deficien allele) has thymine- adenine (TA) repeats within the promoter region of UGT1A1, results in decreased promoter activity.
UGT1A1*1/*36	5/6 Recommendation: Reduced risk of neonatal hyperbilirubinemia	Patient with five thymine-adenine (TA) repeats, and is associated with increased promoter activity of the gene and a reduced risk of neonatal hyperbilirubinemia, a common and typically benign condition.

Figure 3: Report of irinotecan dosage

Test Results

CLINICAL ACTION	DRUG	GENE	GENOTYPE	PHENOTYPE	DRUG RESPONSE			EVIDENCE
					TOXICITY	DOSAGE	EFFICACY	
✗	Amitriptyline	CYP2C19	*2/*2	Poor Metabolizer	--	↓	--	CPIC,L1
		CYP2D6	*10/*10	Intermediate Metabolizer	--	↓	--	CPIC,DPWG,L1
✗	Atorvastatin	APOE	CC(rs7412)	--	--	--	↓	L2-b
		CYP3A5	*3/*3	Poor Metabolizer	--	--	↓	L3
		SLCO1B1	*1A/*5	Decreased Function	↑	↓	--	CPIC,DPWG,L2-a
✗	Citalopram	CYP2C19	*2/*2	Poor Metabolizer	↑	↓	--	CPIC,FDA,DPWG,L1
		CYP2D6	*10/*10	Intermediate Metabolizer	--	--	--	L3
✗	Clomipramine	CYP2C19	*2/*2	Poor Metabolizer	--	↓	↑	CPIC,DPWG,L1
		CYP2D6	*10/*10	Intermediate Metabolizer	↑	↓	--	CPIC,DPWG
✗	Clopidogrel	CYP2C19	*2/*2	Poor Metabolizer	↑	--	↓	CPIC,FDA,DPWG,L1
✗	Doxepin	CYP2C19	*2/*2	Poor Metabolizer	--	↓	--	CPIC,FDA,L1
		CYP2D6	*10/*10	Intermediate Metabolizer	↑	↓	--	CPIC,DPWG
✗	Escitalopram	CYP2C19	*2/*2	Poor Metabolizer	↑	↓	--	CPIC,FDA,DPWG,L1
✗	Imipramine	CYP2C19	*2/*2	Poor Metabolizer	↑	↓	--	CPIC,DPWG,L2-b
		CYP2D6	*10/*10	Intermediate Metabolizer	↑	↓	--	CPIC,DPWG
✗	Simvastatin	APOE	CC(rs7412)	--	--	--	↓	L2-b
		CYP3A5	*3/*3	Poor Metabolizer	--	--	↑	L3

Figure 4: Comprehensive report