

شرکت سلامت پژوهان آرسام نوژن با همکاری اتحاد زیست شناسان ایران،
کمیته تحقیقات و فناوری دانشجویی دانشگاه علوم پزشکی ایران و انجمن
پزشکی مولکولی ایران
برگزار مینماید:

NGS and Pharmacogenomics: From DATA to Clinical Decision

- سخنران: آقای دکتر سیامک صابر
- Medical Molecular Genetic (MD-Ph.D.)
- Member of working group CLINGENE
- دبیر علمی: دکتر منصوره آکوچکیان
- (Ph.D.) ژنتیک مولکولی، هیئت علمی دانشگاه علوم پزشکی ایران
- دبیر اجرایی: دکتر ودیعه قدسی نژاد
- (Ph.D.) پزشکی مولکولی، رئیس هیئت مدیره شرکت آرسام نوژن

NGS and Pharmacogenomics: From DATA to Clinical Decision

Dr. Siamak Saber (MD,MSc,Ph.D)

- Medical Genetic Specialist
- Member of Working Group of ClinGen



Introduction pharmacogenetic and personalized medicine

Pharmacogenomics, the study of how an individual's genetic makeup influences their response to drugs, is a cornerstone of personalized medicine. Pharmacogenetics originated from intermittent genetic studies that focused on drug responses related to specific gene mutations. Over time, as more pharmacogenetic discoveries came to light, the term pharmacogenetics gained prominence after it was coined by German physician Friedrich Vogel in 1959.

Friedrich Otto Vogel (6 March 1925, Berlin – 5 August 2006, Berlin)



Pharmacokinetic (PK)

Pharmacokinetics is the study of what the body does to a drug. It describes how the drug is absorbed, distributed, metabolized, and excreted (ADME) over time.

1. Absorption

How the drug enters the bloodstream

- oral, IV, IM, subcutaneous, inhalation
- affected by gastric pH, motility, food

2. Distribution

How the drug moves from blood → tissues

- protein binding (albumin)
- body fat, body water
- blood–brain barrier

3. Metabolism

How the body chemically modifies the drug

- Phase I enzymes (CYP450)
- Phase II enzymes (UGT, TPMT, NAT2)
- determines activation or inactivation

4. Excretion

How the drug leaves the body

- kidney (urine)
- liver (bile)
- lungs (volatile drugs)

Pharmacodynamics

Pharmacodynamics describes how a drug exerts its therapeutic effect via interactions with cells of the body. This includes a wide range of biological systems such as the immune system, ion channels and specific receptors – which allow communication between a cell and its environment – and enzymes. Pharmacodynamics influences the efficiency of a patient’s response to a specific drug.

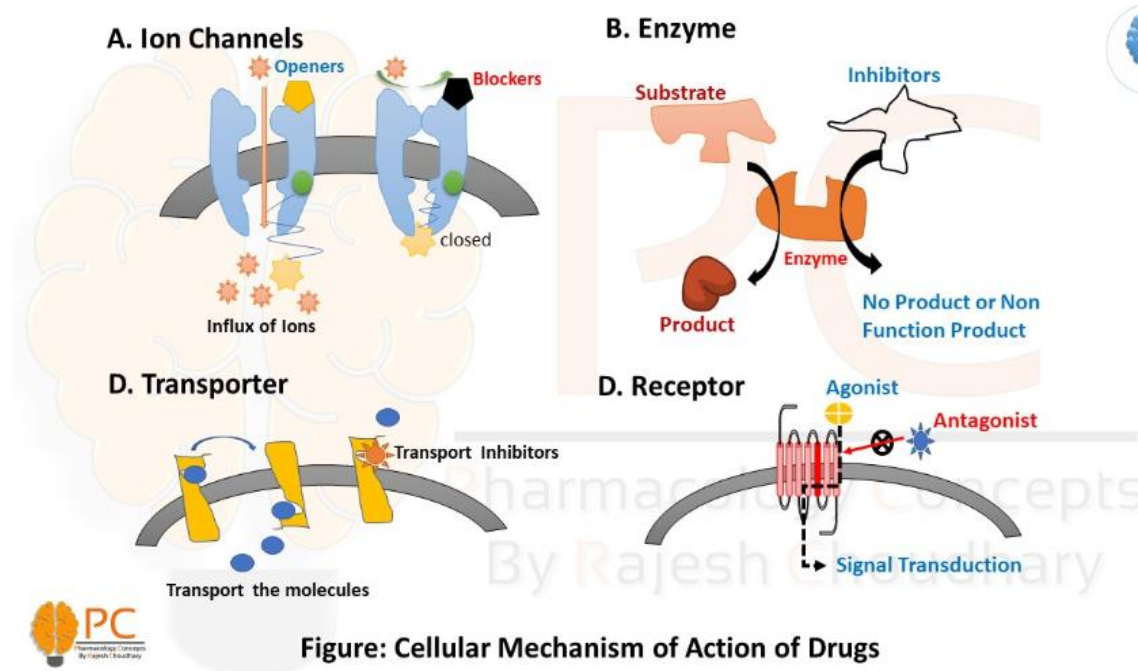


Figure: Cellular Mechanism of Action of Drugs

PHARMACOKINETICS

What the **BODY**
DOES TO THE DRUG



MOVEMENT OF DRUG
THROUGH THE BODY



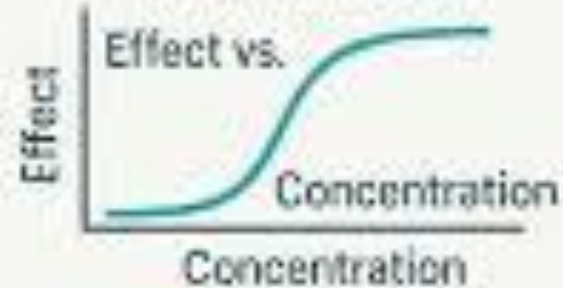
VS

PHARMACODYNAMICS

What the **DRUG**
DOES TO THE BODY



DRUG'S EFFECTS
ON THE BODY



Rapidly-improving sequencing technologies have allowed for large databases of genomic data to be assembled, including the Human Genome Project (2003) in which the entirety of the human genome was sequenced.

The Human Genome Project led to the development of numerous DNA analysis projects and tools including the HapMap Project, which maps the common polymorphisms in the human genome.

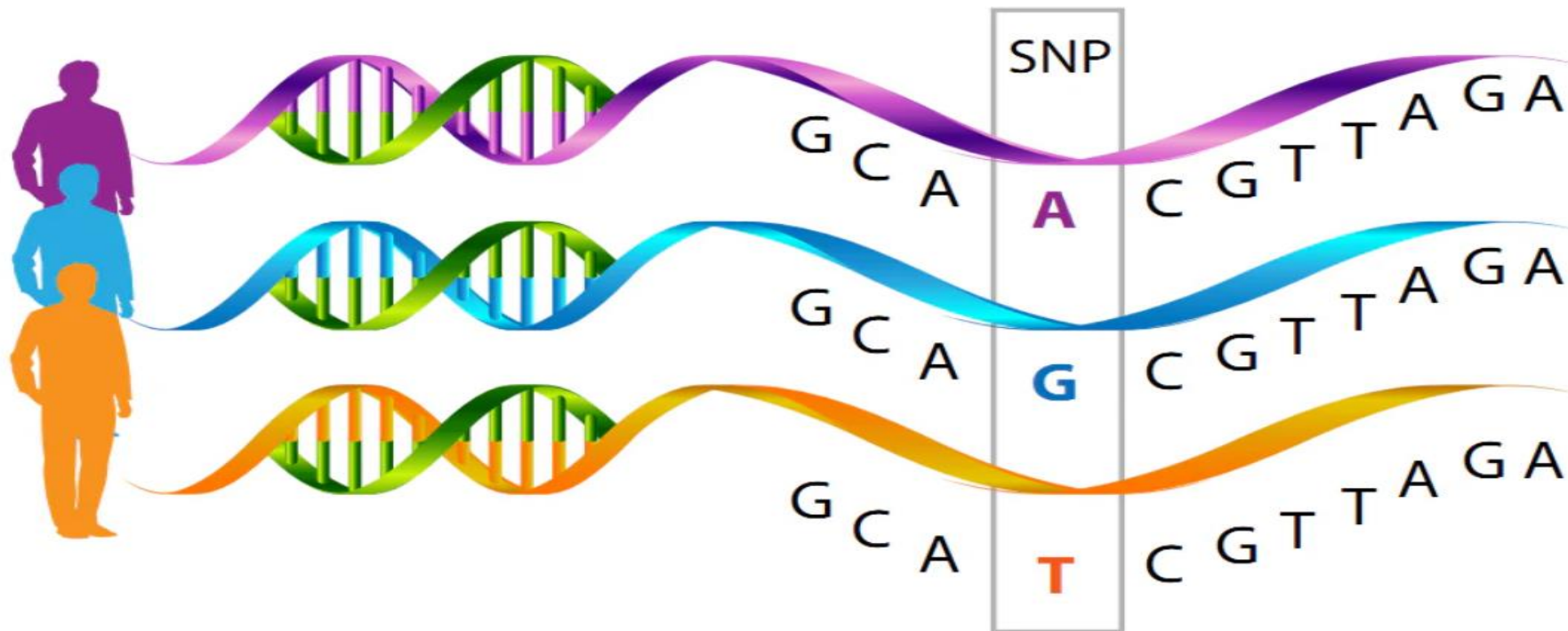
The HapMap Project is essential in pharmacogenomics, particularly as used in **genome-wide association studies** (GWAS), which use statistical tools on genetic variation data to identify the genetic basis of diseases, specific **phenotypes** (i.e. traits), drug reactions and more.

Many pharmacogenomic studies currently use these new techniques and databases, analyzing genetic variations and drug responses in patients to identify gene variants and **biomarkers** (e.g. the product of a gene) that correlate with drug responses.

Human genome \approx 3.2 billion bp, and any two people differ by \sim 3–4 million bp (0.1%).
Mostly **SNPs** (single-nucleotide variants) and small indels.

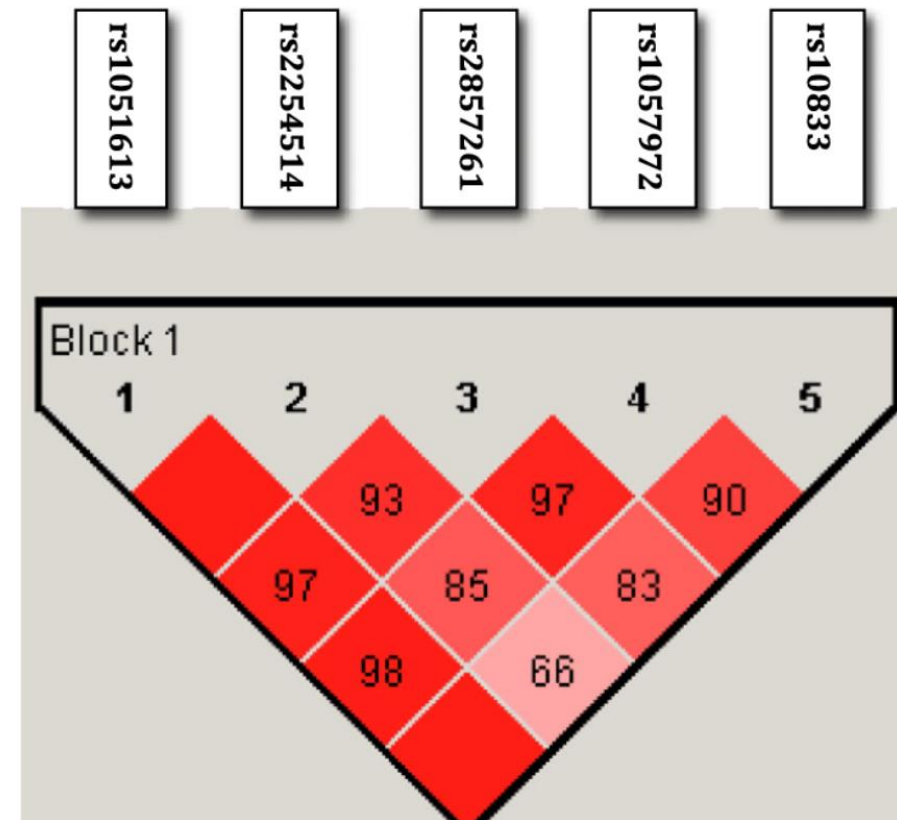
About 1 SNP per kilobase of sequence

The most common type of polymorphism involves variation at a single nucleotide (also called a single-nucleotide polymorphism, or SNP)



Haploview is an important tool for analyzing linkage disequilibrium (LD), constructing haplotypes, and selecting tag SNPs in pharmacogenetics. It plays a key role in designing PGx panels, studying population genetic diversity, and interpreting drug response.

Linkage Disequilibrium (LD) is the non-random association of alleles (genetic variations) at different locations (loci) on a chromosome, meaning they're inherited together more often than by chance, due to physical proximity or shared evolutionary history.



Major SNP Databases:

dbSNP, Ensembl, gnomAD, HapMap, 1000 Genomes

SNP Analysis Software:

Haploview, PLINK, VEP, ANNOVAR, SnpEff

LD and Tag SNP Tools:

LDlink, Haploview, PLINK

<https://ldlink.nih.gov/ldproxy?ref=20898>

Statin and Myopathy

1. Clinical Observation

Some patients developed muscle pain and high CK levels even on normal statin doses → suggested a genetic factor.

2. Genome-Wide Association Studies (GWAS)

Large GWAS studies showed a strong association between the SNP rs4149056 in *SLCO1B1* and a higher risk of statin-induced myopathy. (Haploview, PLINK)

3. Pharmacokinetic Evidence

The risk allele reduces OATP1B1 transporter activity → statins enter the liver less → drug levels increase in blood → higher muscle toxicity.

4. Laboratory & Functional Studies

Cell and animal studies confirmed reduced drug uptake in carriers of the rs4149056 variant.

5. Clinical Confirmation

Multiple clinical studies showed:

- **CC genotype → highest risk**
- **CT genotype → moderate risk**
- **TT genotype → lowest risk**

<https://www.clinpgx.org/>

CPIC guideline for Abacavir and HLA-B

CPIC guideline for Warfarin, CYP2C9, CYP4F2, VKORC1 and
rs12777823

Pharmacogenomics Data Analysis


- Generate PGx data (WES,WGS)
- Quality control (FastQC, Picard, PLINK)
- Variant calling (GATK, DeepVariant, FreeBayes)
- Data analysis (ACMG,ClinGen) , Star allele calling (Haploview)
- and PGx annotation (PharmCAT)
- Interpret genotype → phenotype → drug action
- Create clinical PGx report
- Make clinical decision (dose change, drug switch)

<https://pharmcat.clinpgx.org/examples/pharmcat.example.report.html>

PharmCAT

[Home](#)

[How It Works](#) 

[Using PharmCAT](#) 

[Genes & Drugs](#) 

Examples

[Changelog](#)

[Versioning & Releases](#)

[FAQs](#)

[Disclaimers & Other
Information](#)

[About Us](#)

Named Allele Matcher output

The `Named Allele Matcher` module generates both HTML and JSON files with detailed information about how data in the sample VCF matches up with haplotype definitions.

- [example matcher HTML](#)
- [example matcher JSON](#)

Phenotyper output

The `Phenotyper` module takes data from the `Named Allele Matcher` and combines it with outside call data to assign function and metabolizer values.

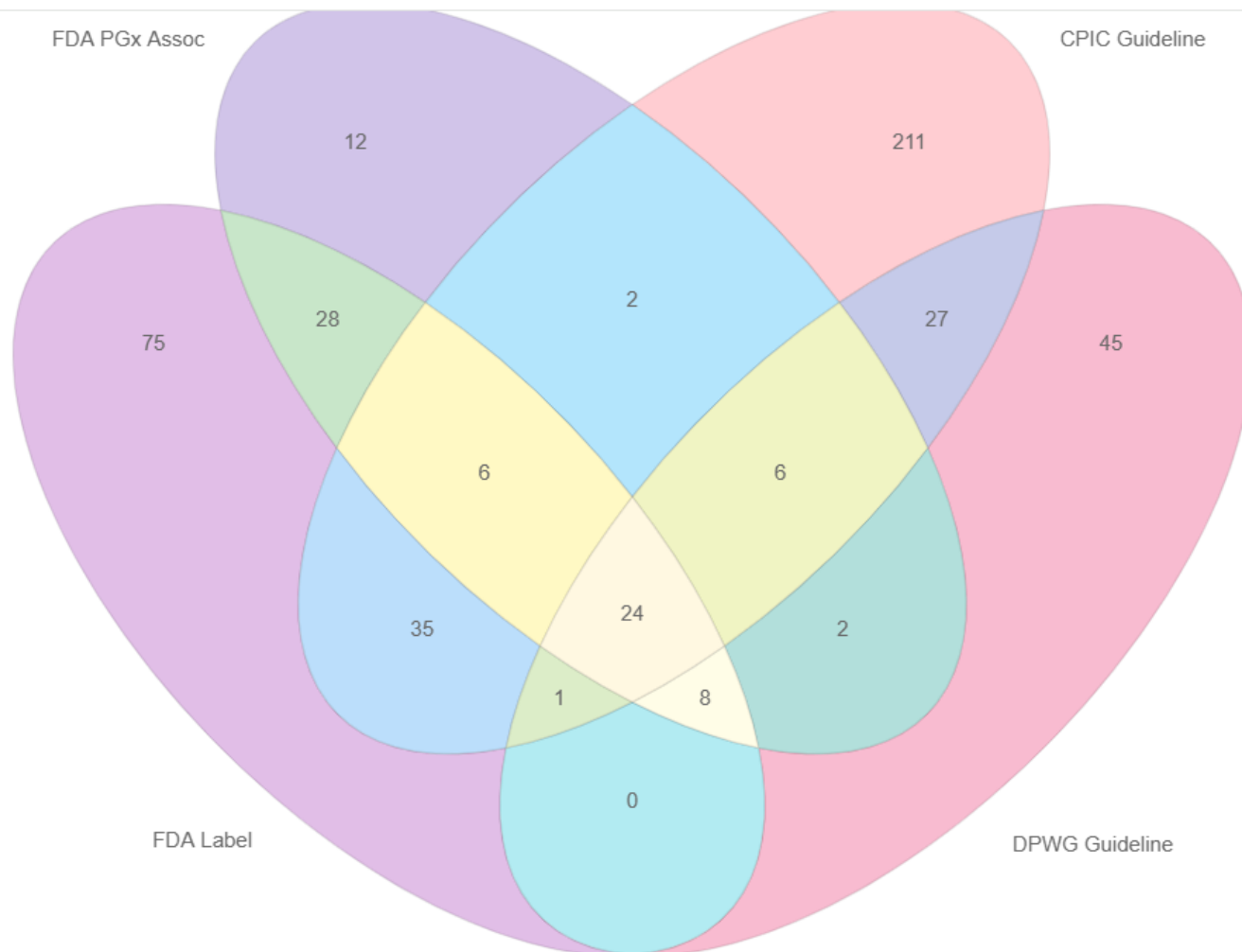
- [example phenotype JSON](#)

Reporter output

The `Reporter` module takes data from the `Phenotyper` and matches phenotypes to information found in CPIC guideline data. This data is visible in an HTML report and also in a JSON file for machine parsing.

- [example report HTML](#)
- [example report JSON](#)
- [example calls-only report TSV](#)

Category	Number of genes Involved
Total pharmacogenes in human genome	~500
Actionable pharmacogenes (clinical practice)	25-40
Genes with CPIC guidelines	25
Genes with PharmGKB (clinpgx)	~44
FDA-recognized variants	~440
High-evidence variants (PharmGKB)	~350-400
Total known PGx variants (all evidence levels)	>1,200



Unique Annotated Gene-Drug Pairs: 482

- CPIC Guideline Pairs = 312
- DPWG Guideline Pairs = 113
- FDA Label Pairs = 177
- FDA PGx Assoc Pairs = 88

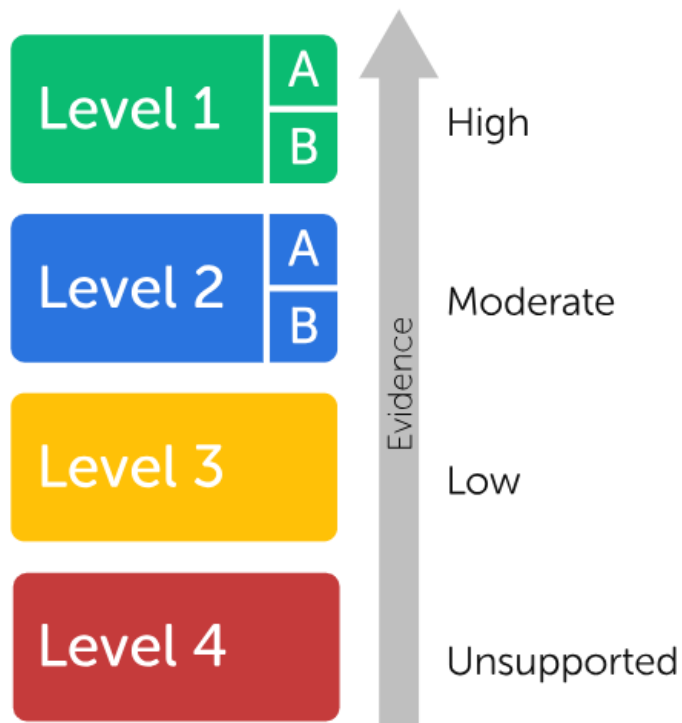
Recommendation Status

Yes = Guideline has recommendation or FDA annotation has action tag ("Dosing Info", "Alt Drug" or "Other Guidance")

No = CPIC guideline level 3 or DPWG "no action"

-- = Pair is not evaluated by the guideline source or not annotated with an action tag

Summary Annotation Levels of Evidence



<https://www.clinpgx.org/pgxGenes>

Data to clinic

Reduce Side Effects & Toxicity

<https://www.clinpgx.org/guidelineAnnotation/PA166104997>

https://youtu.be/-ho-Se249_8

Transform genomic data into actionable clinical decisions for each patient.

1. Reduce Side Effects & Toxicity

2. Choose the Most Effective Therapy

3. Guide Targeted Therapy in Cancer or immunotherapy

Predicting Drug Response (Efficacy)

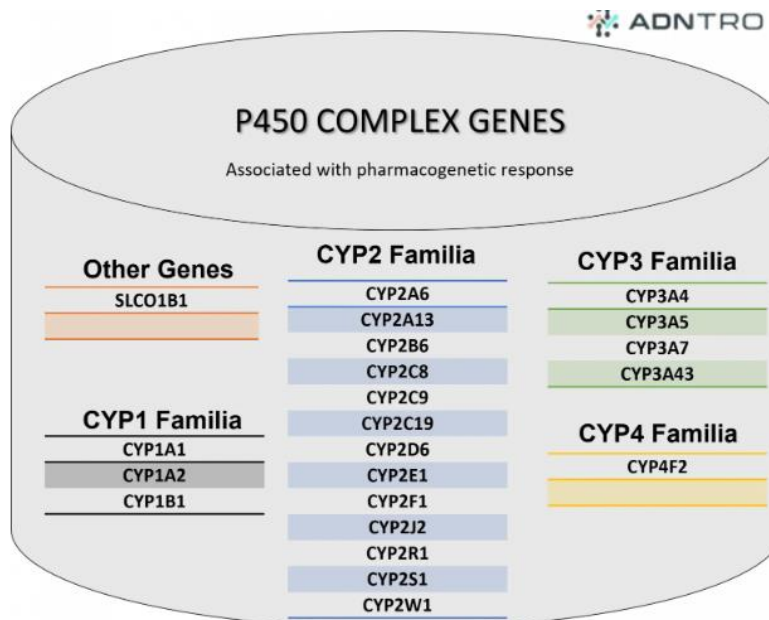
Preventing Drug Toxicity (Safety)

Dose Personalization (Pharmacokinetics)

Pharmacogenomics improves treatment by predicting drug response, preventing toxicity, and personalizing dosing—turning genetic data into real clinical decisions.

Choose the Most Effective Therapy

For instance, cytochrome P450 enzymes (CYP) are key in drug metabolism, and over 85% of people have significant mutations in genes coding for important CYPs (CYP2D6, CYP2C9, CYP2C19, CYP3A4 and CYP3A5). Many CYP mutations affect drug response, demonstrating the importance of metabolic genetics in drug treatments.



Genes of the P450 complex associated with pharmacogenetic response.

Gene Results Overview

Pharmacokinetic Genes (Drug Metabolism / Drug Absorption)	Gene	Genotype	Phenotype	Impact
	ABCB1	A/A	NF	Normal exposure is expected
	ABCB1 C3435T	G/A	NF	Normal exposure is expected
	ABCG2	T/T	PF	Increased exposure to certain medications
	CYP1A2	*1Dc/*1Vc	NM	Normal metabolism is expected
	CYP2B6	*1/*1	NM	Normal metabolism is expected
	CYP2C19	*4B/*7	PM	Risk of increased (↑) drug levels
	CYP2C9	*1/*11	IM	Risk of increased (↑) drug levels
	CYP2D6	*4/*10 (xN)	IM	Risk of increased (↑) drug levels
	CYP3A4/5	*1/*1, *3/*3	NA	Normal metabolism is expected
	SLCO1B1	*1/*1	NF	Normal exposure is expected
	UGT1A4	*3b/*3b	UM	Risk of decreased (↓) drug levels
	UGT2B15	*1/*1	NM	Normal metabolism is expected

Antidepressant Response

Gene	Result	Result
SLC6A4	L(A)/S	Higher odds of gastrointestinal side effects with SSRIs in individuals of European descent
BDNF	Val/Met	More pronounced effect to exercise; Possible higher odds of response to SNRIs
HTR2A	G/G	No known significant clinical impact
MTHFR	C677T: C/T A1298C: A/C	Reduced MTHFR activity and methylfolate production

Attention-deficit/hyperactivity disorder Response

Gene	Result	Result
ADRA2A	C/C	Lower odds of response to methylphenidate for inattentive symptoms of ADHD
COMT	Val/Met	No known significant clinical impact

Antipsychotic Response and Tolerability

Gene	Result	Result
DRD2	C/C	No known significant clinical impact
HTR2C	C/C	No known significant clinical impact
MC4R	A/A	Higher risk of weight gain with certain 2nd generation antipsychotics

Other

Gene	Result	Result
ANK3	C/C	No known significant clinical impact
CACNA1C	G/G	No known significant clinical impact
GRIK1	A/A	No known significant clinical impact
HLA-A *31:01	Positive	Higher risk of skin reactions with carbamazepine
HLA-B *15:02	Negative	No known significant clinical impact
OPRM1	A/A	No known significant clinical impact

Pharmacodynamic Genes
(Drug Targets / Mechanisms)

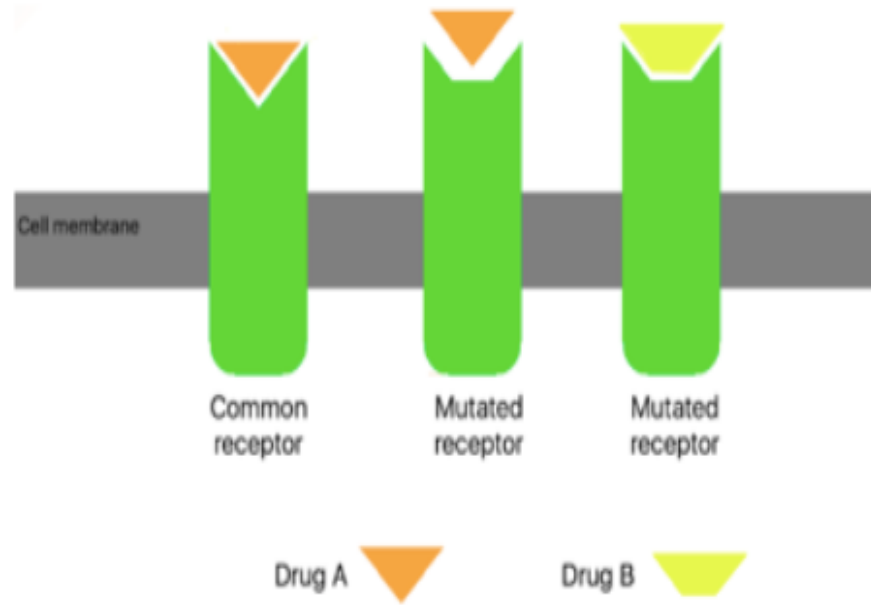
Depression Summary (For Informational Purposes Only)

	Alert / Caution	Standard Options	PGx Guided Options
SSRIs	Citalopram	⊕ ↑	
	Escitalopram	⊕ ↑	
	Fluoxetine	⊕ ↑	
	Paroxetine	⊕ ↑	
	Sertraline	⊕ ↑	
SNRIs		Desvenlafaxine	
		Duloxetine	↑
		Levomilnacipran	
	Venlafaxine	↑	
Other		Bupropion	
		Dextromethorphan/Bupropion	↑
		Mirtazapine	↑
		Nefazodone	
		Trazodone	↑
		Vilazodone	
		Vortioxetine	↑
TCAs	Amitriptyline	↑	
		Desipramine	↑
	Doxepin	↑	
	Imipramine	↑	
		Nortriptyline	↑
		Trimipramine	↑

Depression Augmentation Summary (For Informational Purposes Only)

Alert / Caution	Standard Options	PGx Guided Options
Aripiprazole	↑ ⓘ	
Brexipiprazole	↑ ⓘ	
	Cariprazine	
	ECT	
	Esketamine	
	Exercise	ⓘ
Olanzapine/Fluoxetine	↑ ⓘ	
	Phenelzine	
	Quetiapine	ⓘ
	Selegiline	
	TMS	
	Tranylcypromine	
	VNS	

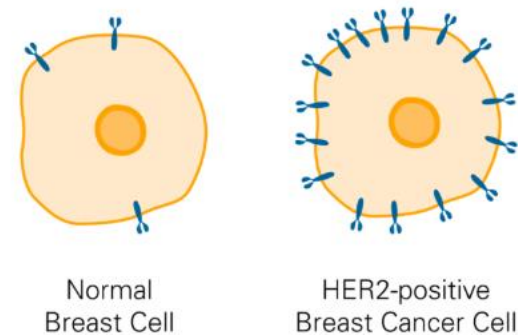
Guide Targeted Therapy in Cancer or immunotherapy



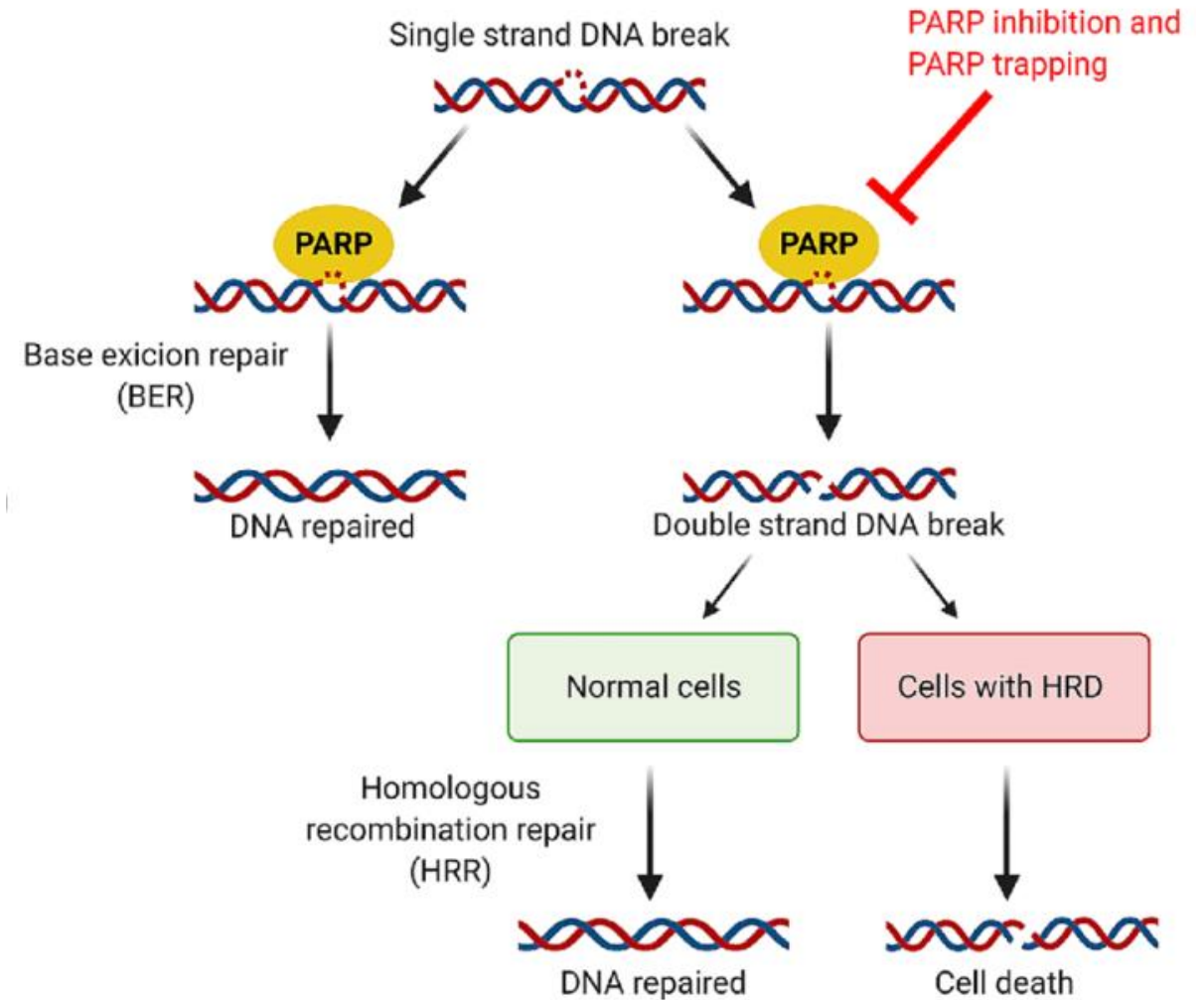
HER2 (Human Epidermal Growth Factor Receptor 2):

HER2-positive cancers have too much of this protein, leading to faster growth.

Therapy: These cancers respond to **anti-HER2 targeted therapies** such as monoclonal antibodies (**trastuzumab, pertuzumab**), tyrosine kinase inhibitors (**lapatinib, tucatinib, neratinib**), and antibody-drug conjugates (**trastuzumab emtansine or trastuzumab deruxtecan**).



- BRCA1/2 Mutations:** Germline (inherited) mutations in the *BRCA1* and *BRCA2* genes impair DNA repair.
 - Therapy:** Patients with these mutations and HER2-negative advanced breast cancer may be candidates for **PARP inhibitors** (e.g., **olaparib**, **talazoparib**), which use the concept of synthetic lethality to target the tumor cells. Platinum-based chemotherapy agents may also be more effective.



Mechanism of action of poly (ADP) ribose polymerase (PARP) inhibitors. Single-strand breaks in DNA are repaired through base excision repair mediated by PARP enzymes. Inhibition of PARP or trapping of PARP on the DNA by PARP inhibitors, result in double-strand breaks in DNA. In normal cells harboring the homologous recombination repair mechanism, doublestrand breaks are repaired and the cell survives. In cells with an homologous recombination deficiency (HRD), including breast cancer (*BRCA* 1 and 2 mutations), this repair mechanism is absent leading to accumulation of double-strand breaks and cell death

Case Presentation

A 58-year-old female patient with breast cancer, diagnosed with HER2-positive breast cancer, has been prescribed a targeted therapy regimen, including trastuzumab (Herceptin).

However, she experiences severe side effects, including fatigue, cardiac toxicity, and low white blood cell count after two cycles of the medication.

Initial assessment and medication history

The patient was started on trastuzumab as part of her chemotherapy protocol after her HER2-positive status was confirmed. However, despite the initial positive response, she begins to experience significant side effects, especially cardiac toxicity (a common issue with trastuzumab), and difficulty tolerating chemotherapy.

The medical team needs to determine whether the side effects are due to the drug or other genetic factors, such as her metabolism or genetic variants that affect drug processing.

Introduction of pharmacogenomic testing

The pharmacist, recognizing the potential role of pharmacogenomics in this case, suggests a pharmacogenomic test to analyze the patient's genetic profile. The test focuses on genetic variants that may influence the metabolism and efficacy of the chemotherapy drugs used in her regimen.

Key tests include:

- a) **CYP450 Enzyme Testing:** These enzymes are responsible for metabolizing many chemotherapy drugs, including trastuzumab. Variants in these genes may lead to slower metabolism, resulting in drug accumulation and side effects.
- b) **Her2 Gene Amplification Test:** Determines whether the patient's HER2 gene is overexpressed, which is necessary for trastuzumab efficacy.
- c) **Pharmacokinetic Profile of Trastuzumab:** Identifying how genetic variations might affect the drug's absorption, distribution, metabolism, and excretion in the body.

The results of the pharmacogenomic tests reveal several key findings:

- 1. HER2 Gene Amplification Confirmed:** The patient has a high level of HER2 overexpression, confirming that trastuzumab is an appropriate treatment for HER2-positive breast cancer. Therefore, the issue likely lies in drug side effects, not in drug efficacy.
- 2. CYP2D6 Genotype:** The test indicates that the patient has a polymorphism in the CYP2D6 gene, which is crucial for metabolizing several chemotherapy drugs. The patient's variant leads to poor metabolism of trastuzumab, resulting in higher drug concentrations in the bloodstream. This genetic variation explains the intense side effects, particularly the cardiac toxicity and immune suppression.
- 3. Drug Interaction Risk:** Additionally, the patient is taking an over-the-counter anti-inflammatory drug (NSAID) for pain, which may further inhibit CYP2D6 activity, exacerbating the side effects of trastuzumab.

Pharmacist's role and interventions

Based on the Pharmacogenomic findings, the pharmacist plays a pivotal role in adjusting the patient's treatment regimen:

- 1. Alternative Treatment Plan:** The pharmacist recommends modifying the chemotherapy regimen by switching to an alternative medication with a different metabolic pathway, such as pertuzumab or lapatinib. Both are effective for HER2- positive breast cancer but are metabolized differently and are less likely to cause cardiac toxicity.
- 2. Adjusting Dosage:** The pharmacist works with the oncologist to reduce the trastuzumab dose, taking into account the patient's poor CYP2D6 metabolism, which could help reduce drug accumulation and mitigate side effects.
- 3. Ongoing Monitoring:** The pharmacist sets up regular follow-up appointments to monitor the patient's response to the new treatment, ensuring that drug levels remain within a therapeutic range and side effects are manageable.

<https://www.oncokb.org/>

<https://www.clinpgx.org/>

<https://www.cbioportal.org/>

<https://gtexportal.org/>

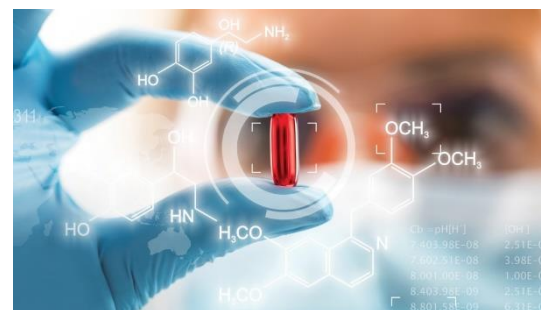
<https://www.deciphergenomics.org/>



همین الان با اسکن QR کد وارد کانال وینار شو!



منابع تکمیلی وینار (جلسه ضبط شده، فایل پاورپوینت وینار و ...)
در این کانال قرار میگیره.
با تکمیل فرم عضویت در باشگاه و شرکت در نظر سنجی وینار میتونین
آرسام نوژنی بشین!



اینستاگرام: **Arsam.Nogene**

کانال تلگرام: **Arsam.Nogene**

مکان: دانشگاه علوم پزشکی ایران، مرکز رشد و فناوری سلامت، ساختمان شماره ۲

سایت شرکت: **Arsamnogene.com** شماره تماس: ۰۹۲۲۲۳۰۳۸۸۰