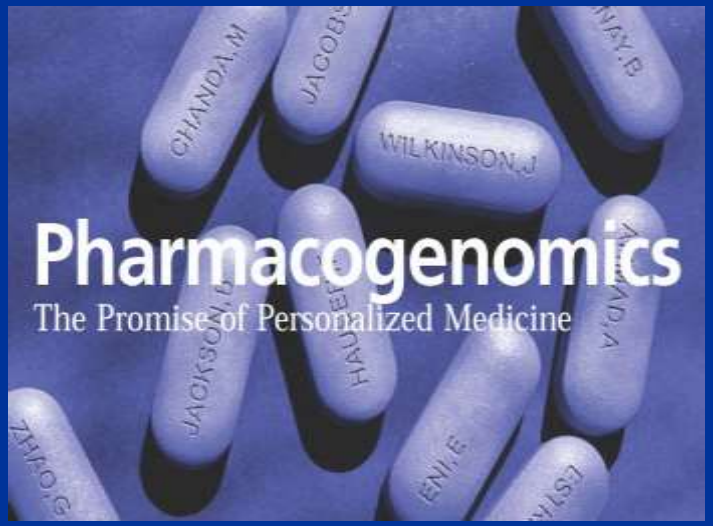
# Pharmacogenetics

"Percision Medicine"

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**Faculty of Medicine-Mutah Uni**

- The **human genome project** has led to an **explosion of genetic information** that is freely available to identify polymorphisms that may determine drug response

in 2004

Ex⇒ PCR, Molecular techniques in general

- **Advances in molecular genetics and genotyping technologies** during the last two decades have led to identification of many polymorphisms in **phase I and phase II drug metabolising enzymes, drug targets, and in drug transporters**

From Blood, Saliva

⊕ Imperical therapy ⇒ giving the drug based on it's genetic type

specialized drug for specific people.

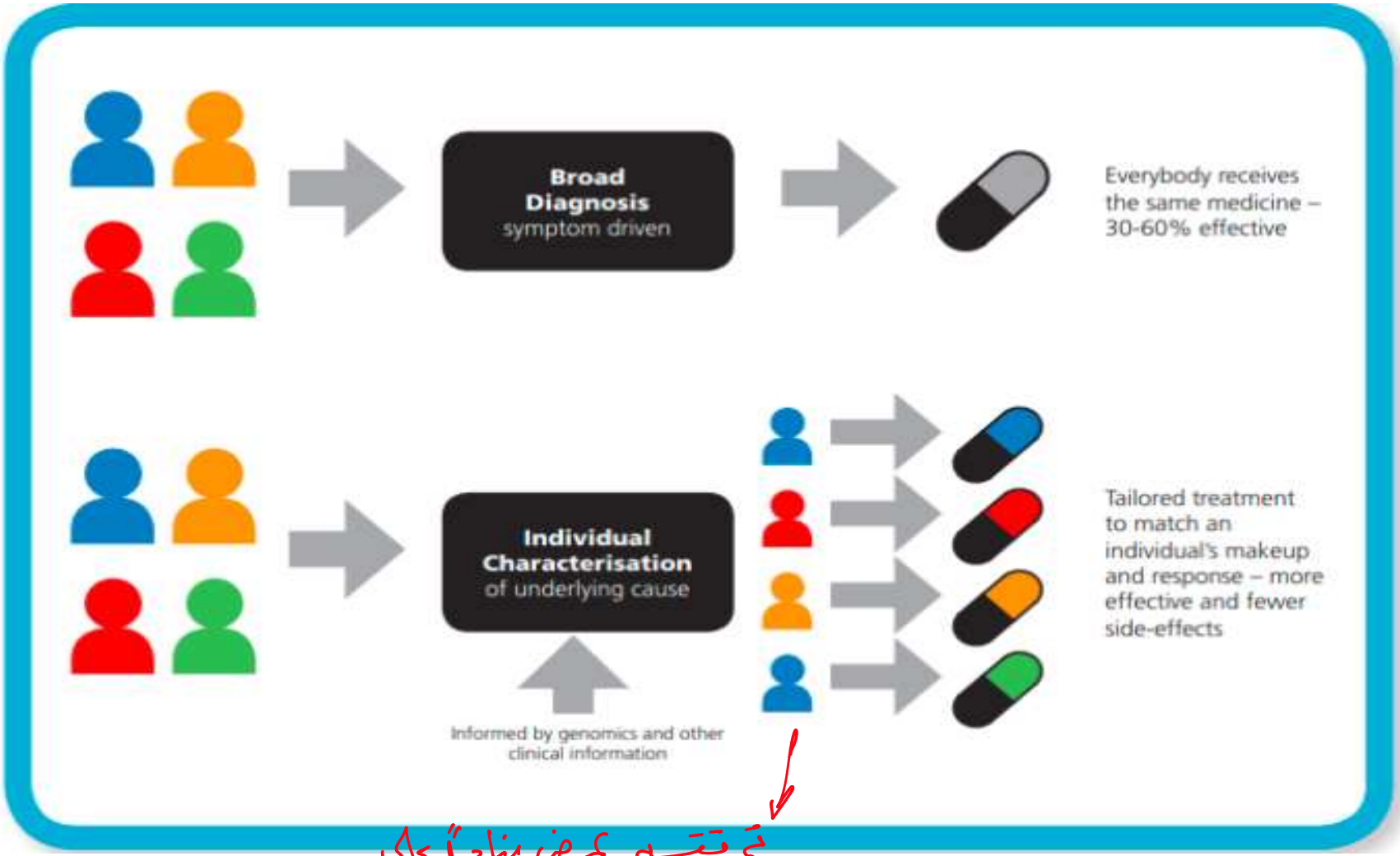
⊕ Polymorphism may occur in receptors and ph.kinetics, ph.dynamics ...etc → Variations in single base or Whole Sequence in DNA

# Individual Variation in Response to Drugs

Not All the people have the Same genetic Structure

- How individuals in a population are expected to respond to a fixed dose of drug?
- Inter-individual variability:
  - Some show less than usual response
  - Most show usual response
  - Others show more than usual response

"Some people may have lack of efficacy based on its genophenotype"




تم تقسيم المرض بناءً على
عدة عوامل. ويعطي dose معيّن
و دواء معيّن لينا سبه بشخص
"genotype"

# Factors Determine Response to Drugs

☺ it's very new concept.

- **Environmental**

  (Age, sex, race, concomitant diseases, diet, smoking, alcohol)

- **Genetic** (polymorphisms drug metabolising enzymes, receptors, drug targets)

# Pharmacogenetics/Pharmacogenomics

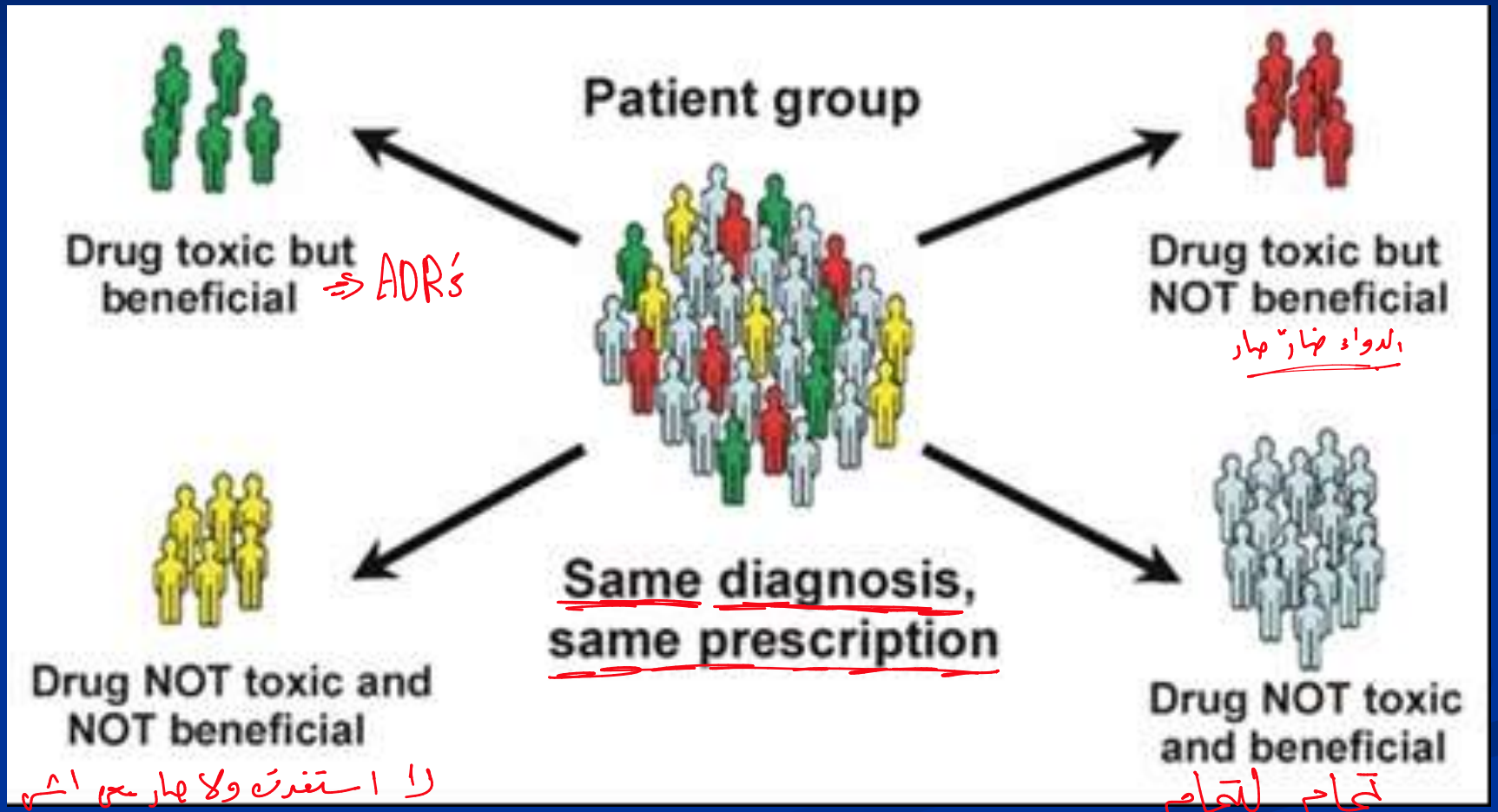
- **Pharmacogenetics:** is study of **variation in drug response due to heredity** & is used in relation **to genes determining drug metabolism**
- **Pharmacogenomics** is a **more general term**; it refers to research area that comprises **all genes in the human genome that may determine drug response**

"All genome" ex.s Target, receptor

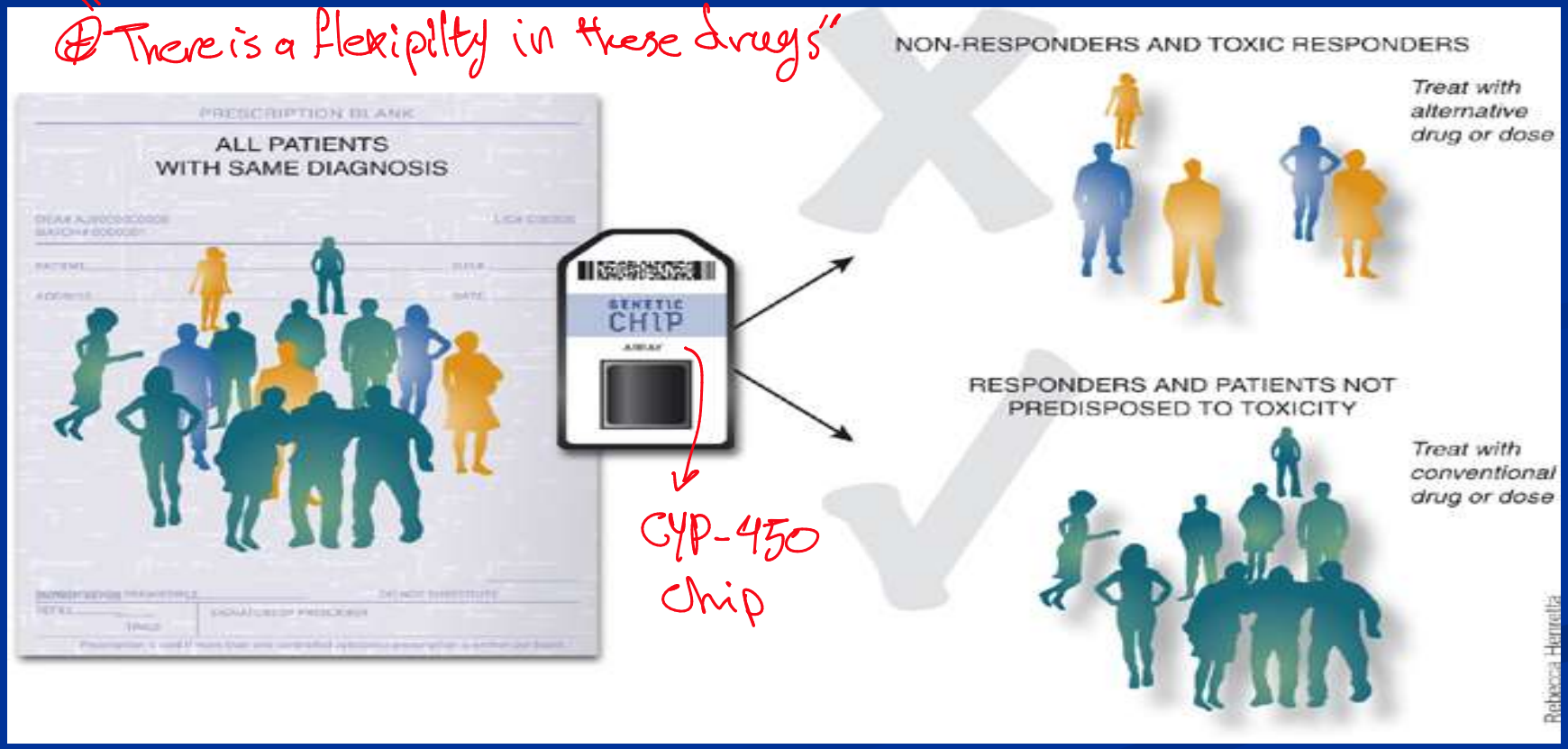
# Benefits of Pharmacogenetics/Pharmacogenomics

- **The concept "The right medicine to the right patient" is the basis of pharmacogenetics (personalised or individualised medicine)**
- **Ultimate goals are to improve clinical therapeutic outcome by:**
  - **Increasing drug efficacy**
  - **Increasing safety of drugs** e.g. reducing incidence of ADRs

# Personalised or Individualised Medicine



# Pharmacogenomic approach to personalized medicine. Drug therapy is chosen for each patient based on their particular genetic profile



- Polymorphisms can occur in any gene that encode:
  - Drug metabolising enzymes
  - Drug transporters
  - Drug targets and receptors

# Genetic polymorphisms of drug metabolising enzyme genes

- The majority of **phase I and phase II drug metabolising enzymes** are polymorphic
- **The cytochrome P450 (CYP) enzymes** are the most important group of **phase I enzymes**
- Polymorphisms in cytochrome P450 genes can cause enzyme products with **abolished or reduced or increased enzyme activity**

# Cytochrome P450 enzymes

Major Pathway

Minor Pathway

depends on

- All genes that encode for families 1-3 are polymorphic & their capacity to metabolise drugs depends on the **functional importance and frequency of variant alleles**

@ cyp4502C9 => Warfarine Metabolism

@ Frequency of Allels => Common or Rare.

# CYP450 Enzymes

- CYP2D6 ⇒ Metabolism of 25% of All drugs ⇒ Antidepresent → SSRI selective serotonine Receptor Inhibitor for "Arrythmia" → Analgesics.
- CYP2C9
- CYP2C19

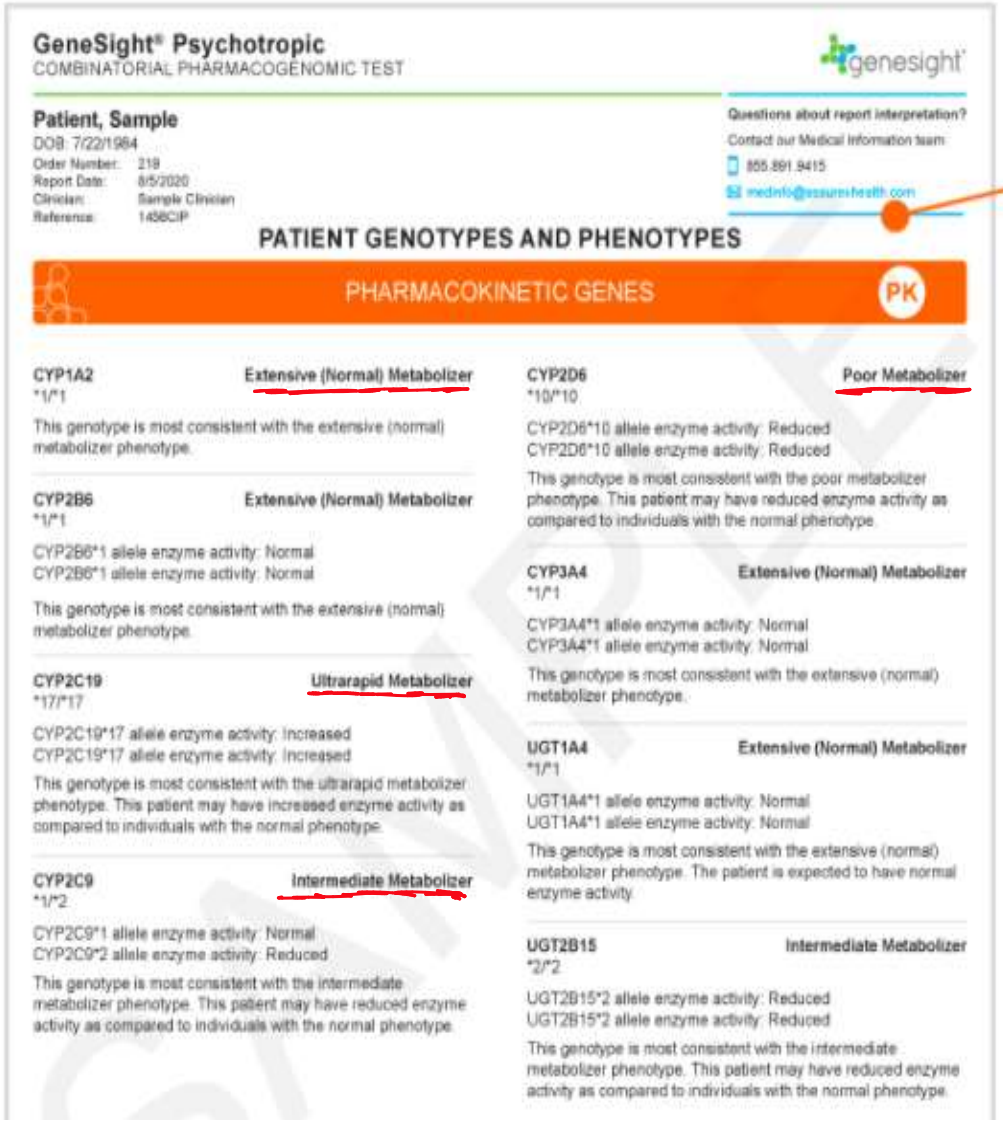
# CYP2D6

- **CYP2D6** contributes to metabolism of large of medications about **25%** **of all drugs**, including:
  - **Antidepressants (TCAs, SSRIs)**
  - **Antiarrythmics**
  - **Analgesics**

# CYP2D6 Phenotypes

- **Poor metabolisers( PM):** lack functional enzyme
- **Intermediate metabolisers (IM):** carry two alleles that cause reduce activity
- **Extensive metabolisers ( EM):** have two normal alleles
- **Ultra-rapid metabolisers (UM):** multiple gene copies

- **Poor metabolisers** **can experience adverse effects** when treated with **standard dose**
- **Ultra-rapid metabolisers** require **high doses of drugs**



**GeneSight® Psychotropic**
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

**Patient, Sample**
DOB: 7/22/1984
Order Number: 219
Report Date: 8/5/2020
Clinician: Sample Clinician
Reference: 1456CIP

Questions about report interpretation?
Contact our Medical Information team
855.891.9415
medinfo@assurehealth.com

## PATIENT GENOTYPES AND PHENOTYPES

### PHARMACOKINETIC GENES (PK)

**CYP1A2** — **Extensive (Normal) Metabolizer**
*1/*1

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

**CYP2B6** — **Extensive (Normal) Metabolizer**
*1/*1

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

**CYP2C19** — **Ultrarapid Metabolizer**
*17/*17

CYP2C19*17 allele enzyme activity: Increased
CYP2C19*17 allele enzyme activity: Increased

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

**CYP2C9** — **Intermediate Metabolizer**
*1/*2

CYP2C9*1 allele enzyme activity: Normal
CYP2C9*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

**CYP2D6** — **Poor Metabolizer**
*10/*10

CYP2D6*10 allele enzyme activity: Reduced
CYP2D6*10 allele enzyme activity: Reduced

This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

**CYP3A4** — **Extensive (Normal) Metabolizer**
*1/*1

CYP3A4*1 allele enzyme activity: Normal
CYP3A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

**UGT1A4** — **Extensive (Normal) Metabolizer**
*1/*1

UGT1A4*1 allele enzyme activity: Normal
UGT1A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

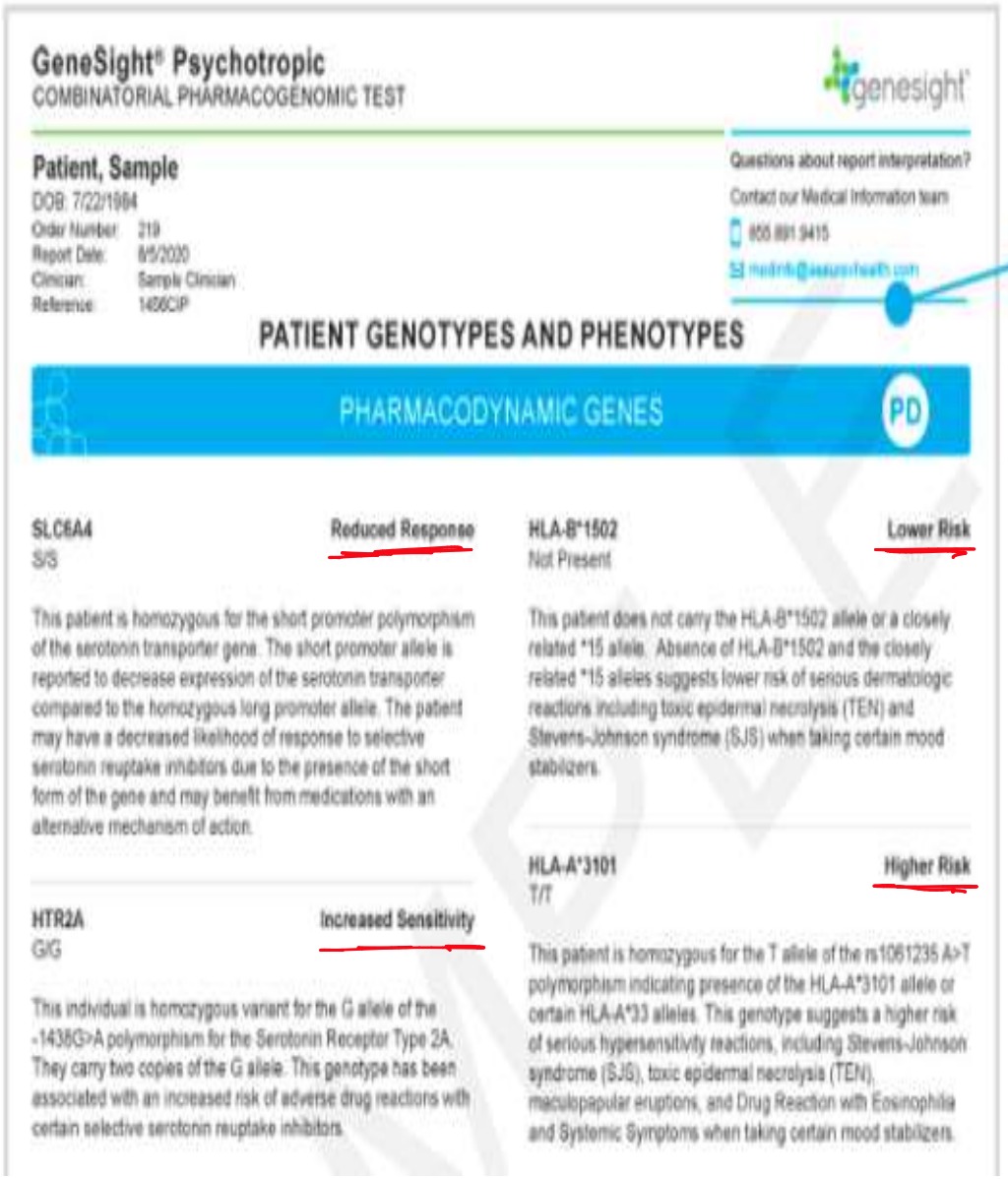
**UGT2B15** — **Intermediate Metabolizer**
*2/*2

UGT2B15*2 allele enzyme activity: Reduced
UGT2B15*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

## Pharmacokinetic Genes

Pharmacokinetic genes provide information on the metabolism of medications.



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## PATIENT GENOTYPES AND PHENOTYPES

### PHARMACODYNAMIC GENES (PD)

**SLC6A4** — **Reduced Response**
S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

**HTR2A** — **Increased Sensitivity**
G/G

This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.

**HLA-B*1502** — **Lower Risk**
Not Present

This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests lower risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

**HLA-A*3101** — **Higher Risk**
T/T

This patient is homozygous for the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

## Pharmacodynamic Genes

Pharmacodynamic genes provide information on how DNA may impact response to some medications.

* it is advised to make a genotyping test to make sure that the drug works. (if possible)

# Depression

- **Tricyclic antidepressants are metabolised by CYP2D6**
- Disposition of **nortriptyline** is related to **number of active CYP2D6 alleles** and
- Dose required to **obtain same plasma drug concentrations** **varies between subjects with different CYP2D6 phenotypes**

- **Ultra-rapid metabolisers** needed **a 10-fold** larger dose of **nortriptyline** than **poor metabolisers** to achieve the same plasma concentration
- **Ultra-rapid metabolisers** require **500 mg** of **doses** compared to **50 mg** in **poor metabolisers**

- Genetic polymorphisms of CYP2D6 **gene may be associated with ADRs** and clinical response to antidepressants
- **30% of patients with ADRs** to antidepressants were **PMs** → Poor Metabolizers
- High incidence of **UMs** among **non-responders (20%)**

# CYP2C9

- **CYP2C9** metabolises a wide range of drugs
- Including drugs with narrow therapeutic indices such as:
  - **Warfarin**
  - **Phenytoin**
  - **Non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen, diclofenac and celecoxib**

# Warfarin and Bleeding

- **Warfarin** is one of the most widely prescribed oral anticoagulant drugs
- **It is used for:**
  - Prophylaxis and treatment of venous thromboemolism
  - Treatment of deep vein thrombosis (DVT)
  - Atrial fibrillation (AF)
  - In patients with prosthetic heart valves

# Warfarin and Bleeding

- The main complication of warfarin therapy is **haemorrhage** ⇒ Bleeding
- Genetic polymorphisms in **CYP2C9** gives rise to variants with altered enzymes activity
- Two allelic variants **CYP2C9*2** (Arg144Cys) and **CYP2C9*3** (Ile359Leu) show **12%** and **5%** of enzyme activity of the wild type **CYP2C9*1** allele, respectively, and are associated with **decreased warfarin dose requirements & increased risk of bleeding**

Reduce the dose

Reduce more the dose

Normal

@warfarin clinic ⇒ genotyping of your genes to know which drug suits you!

# Peptic Ulcer

- **Proton pump inhibitors (PPIs)** are used for treatment of **gastric acid related diseases** such as **peptic ulcers, gastro-esophageal reflux disease (GERD) & in combination with antibiotics (amoxicillin & clarithromycin) for eradication of *Helicobacter pylori* (Hp)**
- **CYP2C19** metabolises several PPIs including **omeprazole** and **lanzoprazole**
- Plasma concentrations of **omeprazole**, depend on patient's **CYP2C19 phenotype**

# AmpliChip CYP450 Array

- **The AmpliChip CYP450** Test provides comprehensive detection of gene variations including **deletions and duplications** for the **CYP2D6** and **CYP2C19 genes**

# Genetic Polymorphisms of Drug Metabolising Enzyme Genes

- With respect to **phase II enzymes**, the most important polymorphisms occur in ***N*-acetyltransferase-2 (NAT-2)** and **thiopurine methyltransferase (TPMT)**
- **NAT-2** is involved in the metabolism of **isoniazid and sulphamethoxazole**

↓ TB

↓ Antibiotic

# Acetylation

- Most individuals are either **rapid or slow acetylators**, but proportion varies between races
- **The percentage of slow acetylators:**
  - **90% in North African**
  - **50% in Caucasian**
  - **10% in Asian populations**

# Thiopurine S-methyltransferase (TPMT)

- **TPMT** catalyzes methylation of **thiopurine drugs** such as **6-mercaptopurine** & **azathioprine**
- These drugs are commonly used in treatment of **acute lymphoblastic leukaemia (ALL), autoimmune diseases, inflammatory bowel diseases, in organ & tissue transplantation**
- **Clinical testing** for TPMT genetic polymorphisms is available

- **It has been shown that:** Frequency Alleles

  - **90%** of population exhibit **high TPMT activity**
  - **10%** show **intermediate activity**
  - **0.3%** have **low or absent enzyme activity**

↓ Normal dose ? toxicity

Ex ⇒ BM cancer.

# Genetic Polymorphisms in Drug Transporters

- **Transporters** are membrane proteins that play crucial role in absorption, distribution & elimination of drugs
- Genetic polymorphisms can occur in transport proteins & may contribute to **inter-individual variation in drug response**
- **MDR1 (multi-drug resistant) P-glycoprotein-Digoxin**
- **Serotonin transporter-antidepressant response**

# Genetic Polymorphisms in Drug targets and Receptors

- **Drug target genes** including those coding for **receptors, ion channels and specific enzymes** are subject to genetic polymorphisms
- **B2-adrenergic receptor: B2 agonist (salbutamol)**
- **Angiotensin converting enzyme (ACE): ACE inhibitors (lisinopril)**
- **Vitamin K epoxide reductase complex (VKORC): Warfarin**

# Practical Points

- Genetic is an important factor responsible for failure to therapy & occurrence of adverse drug reactions
- The goal of PGx is to **maximize efficacy & minimize toxicity**, based on individual's genetic composition
- Individual variation in response to drug **(some may benefit, other fail to respond to treatment, others may develop adverse effects)**