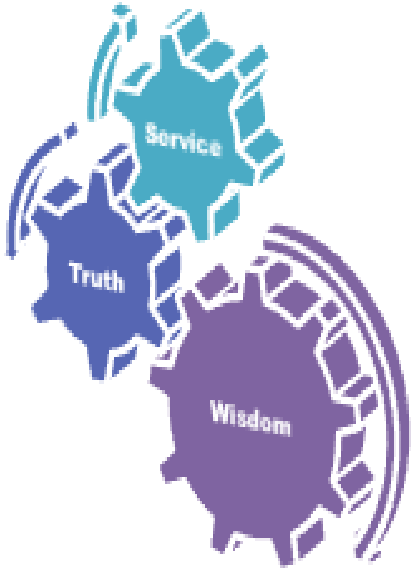
In The Name of ALLAH,
The Most Gracious and The Most Merciful

MOTTO AND VISION

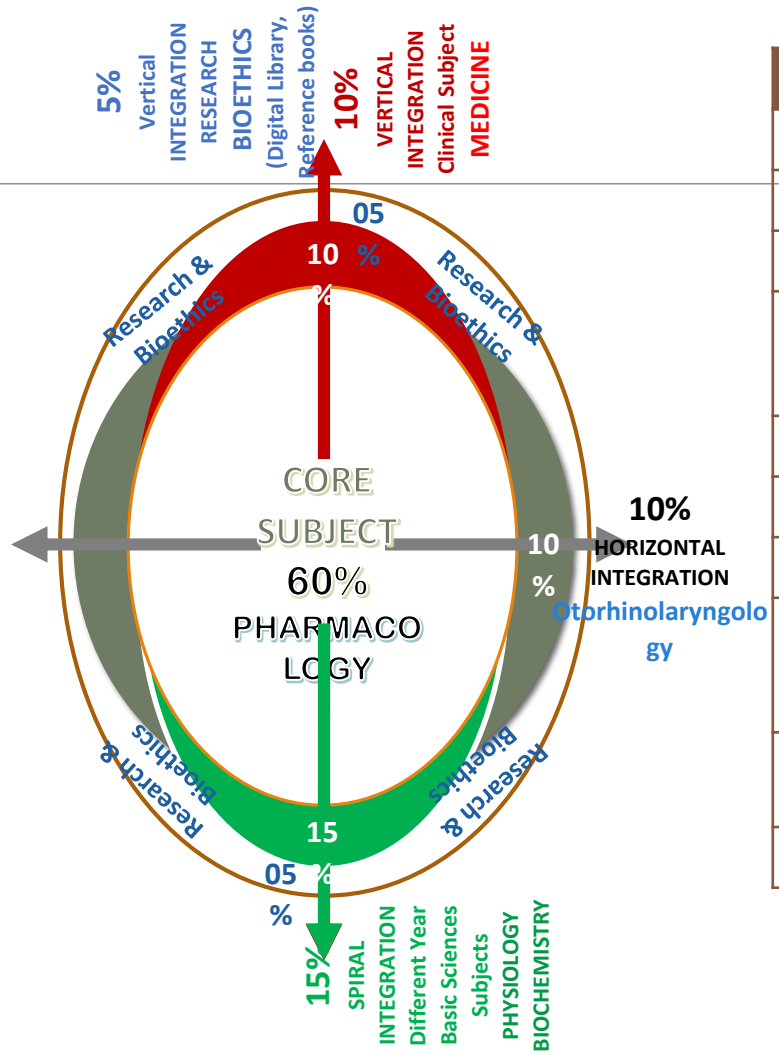


To impart evidence based research oriented medical education

To provide best possible patient care

To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



3rd Year Pharmacology CBL	
Core Subject – 97%	
Pharmacology	
Horizontal Integration – 0%	
Same Year Subjects	• Pathology • Forensic medicine
Vertical Integration – 0%	
Clinical Subjects	• Medicine (3%)
Spiral Integration – 0%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 0%	
Research & Bioethics,Digital library – 3%	

FOUNDATION I MODULE
CBL

SOURCES:

BG KATZUNG BASIC AND CLINICAL PHARMACOLOGY,16TH EDITION

LEARNING OBJECTIVES:

1. Define Pharmacogenetics
2. Explain with the help of examples
3. Explain significance of pharmacogenetics in clinical practice.

CBL

Alina is a 43-year-old patient who noticed skin irritation and dimpling around the side of her right breast one morning. Concerned about her discovery, Alina went to an oncologist the next day. The oncologist requested a mammogram for Alina and upon looking at her results found small, white calcifications clustered together in her breast. Her oncologist then biopsied these calcifications which revealed that the tissue is positive for cancer cells with estrogen receptors. After surgical removal, the doctor recommends long-term treatment with tamoxifen. Before initiating tamoxifen therapy, preemptive testing of Alina's CYP2D6 genotype was also recommended. Alina underwent genotyping and the results came positive for CYP2D6: *1/*10

Questions:

Q1. What is the effect of metabolism on tamoxifen and identify its key pharmacogene.

Q2. Explain the significance of CYP2D6 genotyping in the context of tamoxifen therapy for Alina.

Q3. Categorize Alina’s phenotype based on her genetic testing.

Q4. How might Alina's CYP2D6 genotype influence her response to tamoxifen therapy?

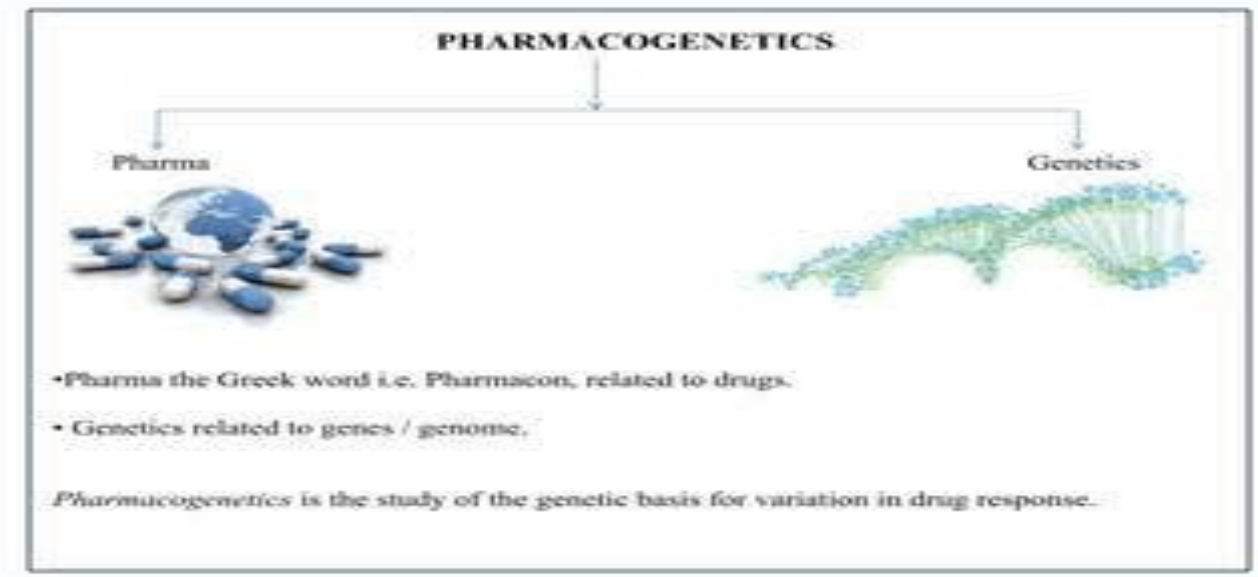
Q5. Explain the importance of integrating pharmacogenetic testing into clinical practice.

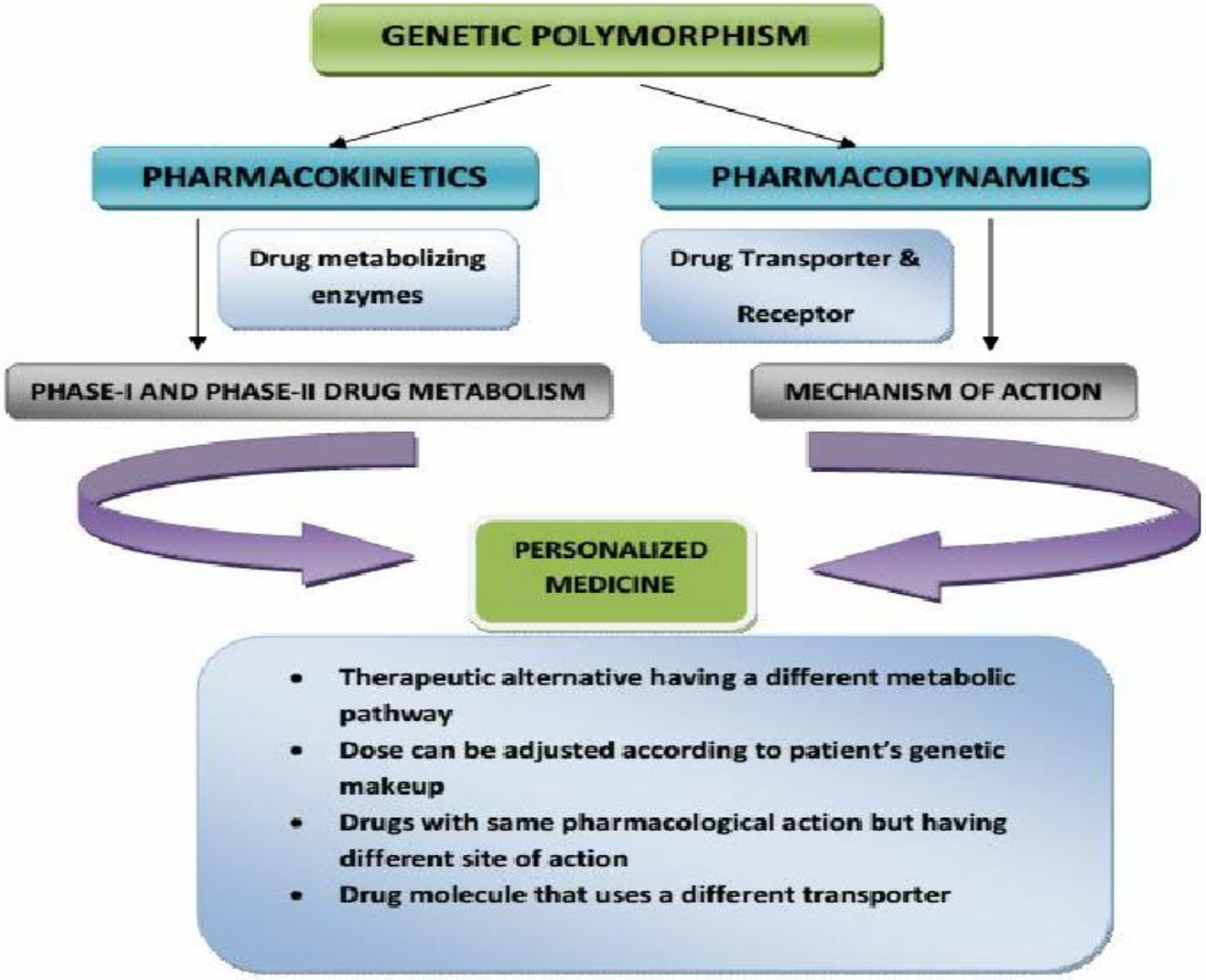
Introduction:

- Pharmacogenetics = Pharma and genetics
  - Pharma is derived from the Greek word i.e. PHARMACON, related to Drugs.
  - Genetics means related to genes / genome.
- Now known as “**PHARMACOGENOMICS**”

Definition:

"..It is the branch of Pharmacology, that deals with the altered drug response shown due to variation in the Genetics.."




GENETIC POLYMORPHISM
PHARMACOKINETICS
PHARMACODYNAMICS
Drug metabolizing enzymes
Drug Transporter & Receptor
PHASE-I AND PHASE-II DRUG METABOLISM
MECHANISM OF ACTION
PERSONALIZED MEDICINE
Therapeutic alternative having a different metabolic pathway
Dose can be adjusted according to patient's genetic makeup
Drugs with same pharmacological action but having different site of action
Drug molecule that uses a different transporter

Some Genetic Variations/Disorders and the altered Drug response:

1. Less active or inactive Cytochrome P450:
   - The system is unable to breakdown and efficiently eliminate the drug from the body which leads to **drug over-dosage** and thus **adverse effects** in patients.
   - E.g.: Slow Hydroxylation of Warfarin cause accumulation of drug and resulting in Warfarin side effects

Cntd..

2. Cytochrome 2C19 Deficiency:

- It is a type of P450, that are liver enzymes.
- The Cytochrome 2c19 catalyzes the hydroxylation of clopidogrel (i.e. an anti-platelet drug)
- Genetic Polymorphism Results in clopidogrel reduced anti-platelet effects.

Some Drugs whose metabolism is affected by P450 Variants:

- Anti-arrhythmics
- Beta – Adrenergic receptor blockers
- Neuroleptics
- Tricyclic Anti-depressants
- Decongestants

Cntd..

3. **Pseudocholinesterases Deficiency:**
   - An enzyme that breaks down cholines.
   - It’s deficiency causes increased sensitivity to certain muscle relaxant drugs (Succinylcholine) used during general anesthesia.
   - Patient will be unable to move or breathe on their own for a few hours after the drugs are administered.
   - Incidence of this deficiency is 1/3000 patients.

Cntd..

4. Glucose-6-Phosphate Dehydrogenase Deficiency:

- It is an enzyme that converts Glutathione to a reduced form, that keeps membrane proteins in operative condition.

- Deficiency leads to altered cell membrane and thus causing hemolysis on administration of some drugs like Anti-malarial, Sulphonamides, Analgesics, Sulphones etc

Cntd..

5. Acetylation:

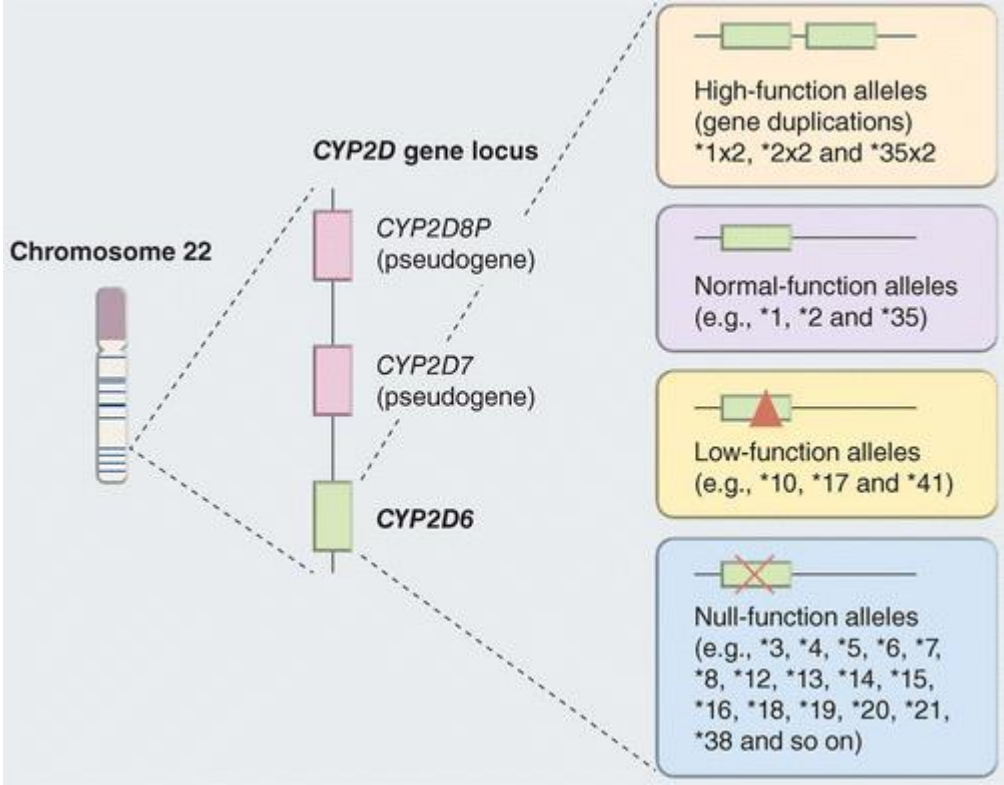
- Defect is less synthesis of **N-acetyltransferase** (liver) Slow Acetylation. Rest, Fast Acetylators!
- Slow Acetylation may lead to higher blood levels of the drug and thus, result in toxic effects.
- Drugs Metabolized by Acetylation:
  - ✓Isoniazid
  - ✓Procainamide (antiarrhythmic)
  - ✓Sulfa drugs (e.g. sulfonamide antibiotics)
  - ✓Dapsone (anti-leprosy, antiparasitic)

Genotype for CYP2D6:

CYP2D6 alleles *3 , *4 , *5 *6
= are non functional alleles

*10,*17,*41 = reduced functional

*1,*2 = fully functional



Phenotypes for CYP2D6:

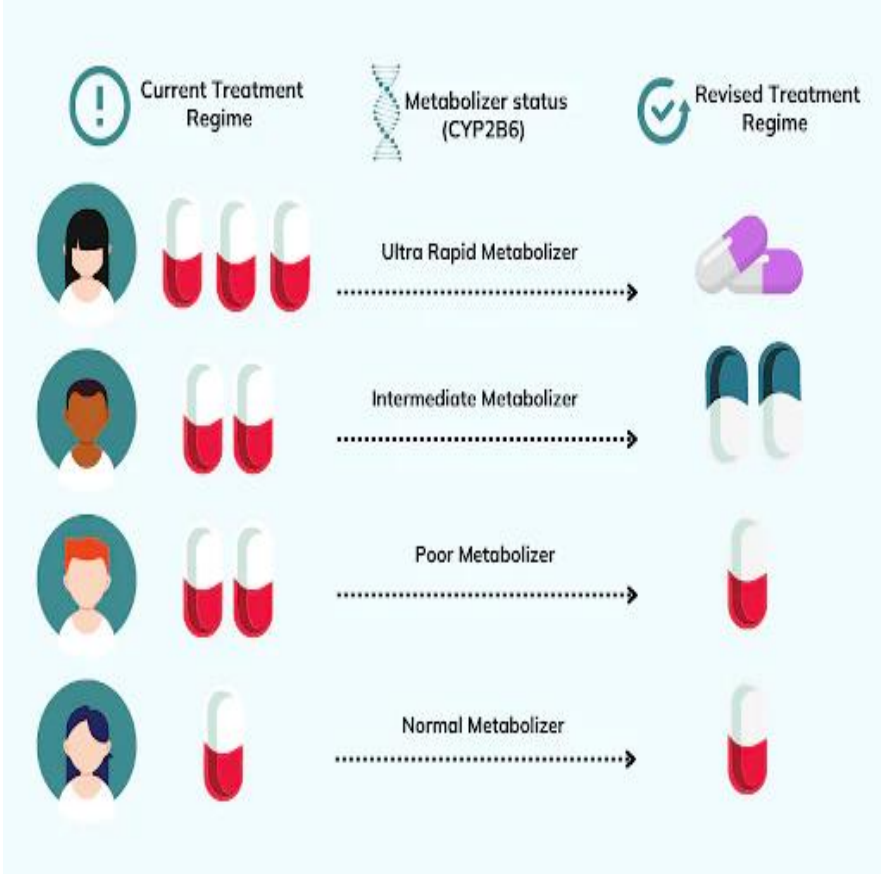
The sum of allelic activities scores typically ranges between 0 and ≥ 3.0 and is most often used to define phenotypes as follows:

0=PM(poor metabolizer),

0.5=IM,

1.0-2.0=EM,

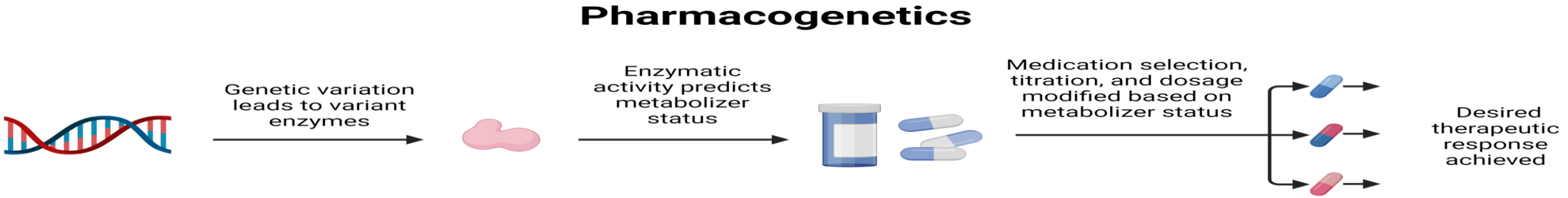
and ≥ 2.0=UM (ultra rapid metabolizer



CYP2D6 Phenotype	Implications	Recommendations for tamoxifen therapy	Classification of recommendation
Ultrarapid metabolizer	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. **Initiate therapy with recommended standard of care dosing** (tamoxifen 20 mg/day).	Strong
Normal metabolizer	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. **Initiate therapy with recommended standard of care dosing** (tamoxifen 20 mg/day).	Strong
Intermediate metabolizer (AS = 1)	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	**Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women**, given that these approaches are superior to tamoxifen regardless of CYP2D6 genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher, but FDA approved, tamoxifen dose (40 mg/day). Avoid CYP2D6 strong to weak inhibitors.	Optional

Significance of Pharmacogenetics:

1. Personalized medicine
2. Optimized Drug Selection
3. Dosing Optimization
4. Reduction of Adverse Drug Reaction
5. Cost Effectiveness



Beneficence

The principle of beneficence is the obligation of physician to act for the benefit of the patient and supports a number of moral rules to protect and defend the right of others, prevent harm, remove conditions that will cause harm, help persons with disabilities, and rescue persons in danger.

It is worth emphasizing that, the language here is one of positive requirements. The principle calls for not just avoiding harm, but also to benefit patients and to promote their welfare.

How To Access Digital Library

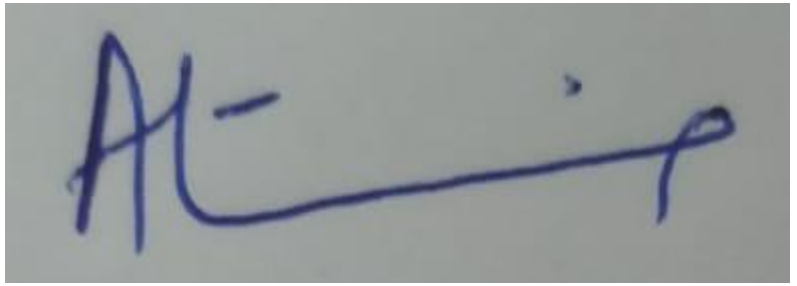
Steps to Access HEC Digital Library

1. Go to the website of HEC National Digital Library.
2. On Home Page, click on the INSTITUTES.
3. A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
4. Select your desired Institute.
5. A page will appear showing the resources of the institution
6. Journals and Researches will appear
7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter keyword to search for your desired journal.

Research articles:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255432/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3099369/




Thank you!